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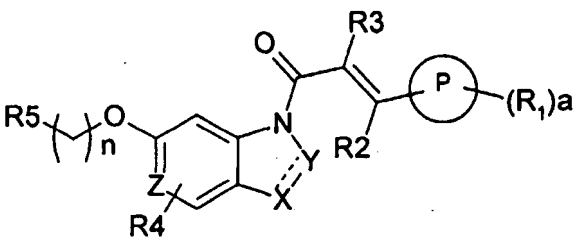

(I)

(57) Abstract: The invention relates to novel cinnamide compounds which have 5-$HT_{2C}$ antagonist activity and have the general formula (I), or is a pharmaceutically acceptable salt thereof: in which P is phenyl or naphthyl; $R^1$ is halogen, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$alkylthio, hydroxy, amino, mono- or di-$C_{1-6}$alkylamino, nitro, CN, $CF_3$, $OCF_3$, aryl, aryl$C_{1-6}$alkyl, aryl$C_{1-6}$alkyloxy or aryl$C_{1-6}$alkylthio; a is 0, 1, 2, 3, 4 or 5; $R^2$ and $R^3$ are independently hydrogen or $C_{1-6}$alkyl; $R^4$ is hydrogen, halogen, $C_{1-6}$alkyl, $C_{1-6}$alkocy, aryl, cyano, halo$C_{1-6}$alkyl or $OCF_3$; Z is carbon or nitrogen; $R^5$ is either: (i) a group $NR^6R^7$ where $R^6$ and $R^7$ are independently hydrogen, optionally substituted $C_{1-6}$alkyl; or (ii) an optionally substituted N-linked heterocycle; or (iii) an optionally substituted C-linked heterocycle; n is 0, 1, 2 or 3 subject to the proviso that n is not 0 when $R^5$ is a group (i) or (ii); ⎓ represents a single or double bond; X and Y are independently $CR^8R^9$ (when ⎓ represents a single bond) or X and Y are independently $CR^{10}$ (when ⎓ represents a double bond) wherein $R^8$, $R^9$ and $R^{10}$ are independently hydrogen or $C_{1-6}$alkyl. Also disclosed are processes for their preparation, compositions containing them and their use in the treatment of CNS and other disorders.

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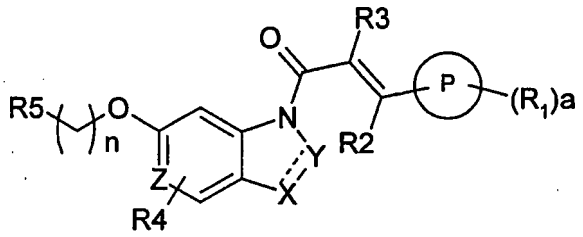
# INDOLINE DERIVATIVES AS 5HT2C ANTAGONISTS

This invention relates to novel cinnamide compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

WO 96/23783, WO 97/48699 and WO 97/48700 all disclose a series of indoline derivatives which are 5-$HT_{2C}$ receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders.

A novel class of compounds has now been found which also possess 5-$HT_{2C}$ receptor activity. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:




(I)

in which:

P is phenyl or naphthyl;

$R^1$ is halogen, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$alkylthio, hydroxy, amino, mono- or di-$C_{1-6}$alkylamino, nitro, CN, $CF_3$, $OCF_3$, aryl, aryl$C_{1-6}$alkyl, aryl$C_{1-6}$alkyloxy or aryl$C_{1-6}$alkylthio;

a is 0, 1, 2, 3, 4 or 5;

$R^2$ and $R^3$ are independently hydrogen or $C_{1-6}$alkyl;

$R^4$ is hydrogen, halogen, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, aryl, cyano, halo$C_{1-6}$alkyl or halo$C_{1-6}$alkoxy;

Z is carbon or nitrogen;

$R^5$ is either:

(i) a group $NR^6R^7$ where $R^6$ and $R^7$ are independently hydrogen, optionally substituted $C_{1-6}$alkyl or aryl$C_{1-6}$alkyl; or

(ii) an optionally substituted N-linked heterocycle; or

(iii) an optionally substituted C-linked heterocycle;

n is 0, 1, 2 or 3 subject to the proviso that n is not 0 when $R^5$ is a group (i) or (ii);
------ represents a single or double bond;
X and Y are independently $CR^8R^9$ (when ------ represents a single bond) or X and Y are independently $CR^{10}$ (when ------ represents a double bond) wherein $R^8$, $R^9$ and $R^{10}$ are independently hydrogen or $C_{1-6}$alkyl.

The following terms, whether used alone or as part of another group, are unless otherwise stated, to be given the following meanings.

The term "halogen" is used herein to describe a group selected from fluorine, chlorine, bromine and iodine.

The term "alkyl" is used herein to describe a straight chain or branched fully saturated hydrocarbon group. "$C_{1-6}$alkyl" refers to alkyl groups having from one to six carbon atoms in all isomeric forms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, sec-pentyl, n-pentyl, isopentyl, tert-pentyl and hexyl.

The term "$C_{1-6}$alkoxy" refers to a straight chain or branched chain alkoxy (or "alkyloxy") group having from one to six carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy, sec-pentoxy, n-pentoxy, isopentoxy, tert-pentoxy and hexoxy.

The term "$C_{1-6}$alkylthio" refers to a straight chain or branched chain alkylthio group having from one to six carbon atoms, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio, sec-pentylthio, n-pentylthio, isopentylthio, tert-pentylthio and hexylthio.

The term "mono- or di-$C_{1-6}$alkylamino" refers to an amino group which is substituted by one $C_{1-6}$alkyl group or an amino group which is substituted by two $C_{1-6}$alkyl groups, the two amino groups being the same or different. Examples of monoC1-6alkylamino include methylamine, ethylamine, propylamine, isopropylamine, butylamine, isobutylamine, sec-butylamine, tert-butylamine, pentylamine, neopentylamine, sec-pentylamine, n-pentylamine, isopentylamine, tert-pentylamine and hexylamine. Examples of di C1-6alkylamino include dimethylamine, diethylamine, dipropylamine, diisopropylamine, dibutylamine, diisobutylamine, disec-butylamine, ditert-butylamine, dipentylamine, dineopentylamine, dihexylamine, butylmethylamino, isopropylmethylamino, ethylisopropylamino, ethylmethylamino, etc.

The term "aryl" is used herein to describe aromatic carbocyclic or heterocyclic groups such as phenyl or naphthyl. Such groups can be optionally substituted by one or more groups such as $C_{1-6}$alkyl, halogen, $C_{1-6}$alkoxy, halo-substituted $C_{1-6}$alkoxy (eg $OCF_3$), halo-substituted $C_{1-6}$alkyl (eg $CF_3$), cyano, or sulphonyl. The aryl group can also be fused to other rings such as a dioxolanyl group.

The term "aryl$C_{1-6}$alkyl" is used herein to describe an aryl group which is linked by a $C_{1-6}$alkyl group. Similarly, the terms "aryl$C_{1-6}$alkyloxy" and "aryl$C_{1-6}$alkylthio" refer respectively to an aryl group which is linked by a $C_{1-6}$alkyloxy or a $C_{1-6}$alkylthio group. Examples include phenoxy and phenethylthio.

The term "halo$C_{1-6}$alkyl" refers to a $C_{1-6}$alkyl group which is substituted by one or more halogen atoms such as fluorine, chlorine, bromine and iodine. Examples include $CF_3$, $CH_3Cl$ and chloromethane.

The term "halo$C_{1-6}$alkoxy" refers to a $C_{1-6}$alkoxy group which is substituted by one or more halogen atoms such as fluorine, chlorine, bromine and iodine. Examples include $OCF_3$, $OCH_3Cl$ etc.

The term "N-linked heterocycle" is used herein to describe a stable non-aromatic 5 - 7 membered ring containing at least 1 nitrogen atom and optionally a further 1 or 2 heteroatoms selected from nitrogen, sulphur or oxygen, wherein the heterocycle is linked to the remainder of the molecule via a nitrogen atom.

The term "C-linked heterocycle" is used herein to describe a stable non-aromatic 5-7 membered ring containing at least 1 nitrogen atom and optionally a further 1 or 2 heteroatoms selected from nitrogen, sulphur and oxygen, wherein the heterocycle is linked to the remainder of the molecule via a carbon atom.

Suitable examples of N-linked or C-linked heterocycles include pyrrolidinyl, piperazinyl, morpholinyl, imidazolidinyl, thiomorpholinyl, piperidinyl and azepanyl. Suitable optional substituents for N-linked and C-linked heterocycles include $C_{1-6}$alkyl, amino, mono- or di- $C_{1-6}$alkylamino, aryl, aryl$C_{1-6}$alkyl, arylamino, hydroxy, $C_{1-6}$alkylamido, hydroxy$C_{1-6}$alkyl, $C_{1-6}$alkoxycarbonyl, halogen, haloC1-6alkyl, a heteroaromatic group such as indole or benzimidazole or a aromatic or non-aromatic heterocycle-$C_{0-6}$alkyl optionally substituted by $C_{1-6}$alkyl. Within the group "aromatic or non-aromatic heterocycle-$C_{0-6}$alkyl" it will be appreciated $C_0$ alkyl indicates a single bond. Examples of aromatic or non-aromatic heterocycle-$C_{0-6}$alkyl include heterocycle (such as piperidine or pyrrolidine), heterocycle-methyl (such as pyridinyl-methyl and benzimidazolyl-methyl) and heterocycle-ethyl (such as

morpholinyl-ethyl and indolyl-ethyl). More than one optional substituent may be present, which may be the same or different, and may be attached to any carbon atom of the heterocycle or, when present, to a nitrogen atom. Where used herein the term "optionally substituted" is also intended to include moieties in which more than one substituent is present on the same carbon atom and includes spiro structures such as 1,4 and 1,5 dioxa spiro compounds. Examples of $R^5$ therefore also include 1,4-dioxa-8-azaspiro[4.5]decyl, 1,5-dioxa-9-azaspiro[5.5]undecyl, 2-oxa,5-aza-bicyclo[2.2.1]heptyl, and 8-aza-bicyclo[3.2.1]octyl.

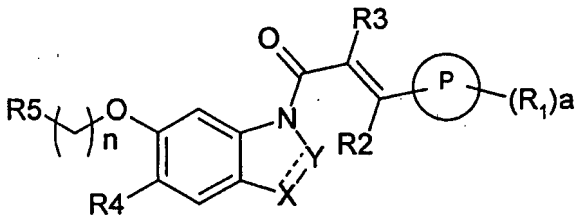
Preferably P is phenyl.

When a is not 0, $R^1$ is preferably halogen (particularly fluoro, chloro or bromo), a $C_{1-6}$alkyl group (particularly methyl), a $C_{1-6}$alkoxy (particularly methoxy) or $OCF_3$. When a is 2 or more the groups $R^1$ may be the same or different. Preferably a is 0, 1, 2, or 3.

When $R^2$ or $R^3$ is $C_{1-6}$alkyl a preferred group is methyl. Preferably $R^2$ and $R^3$ are both hydrogen.

Preferably Z is carbon.

Preferably $R^4$ is hydrogen, halogen (particularly chloro or bromo), $C_{1-6}$alkoxy (particularly methoxy) or $C_{1-6}$alkyl group (particularly methyl). When $R^4$ is a halo$C_{1-6}$alkyl, it is preferably $CF_3$ and when $R^4$ is a halo$C_{1-6}$alkoxy, it is preferably $OCF_3$. Preferably, Z is carbon and $R^4$ is at the 5 position of the indoline or indole ring:




Most preferably, Z is carbon and $R^4$ is a methoxy group at the 5 position of the indoline or indole ring.

When $R^5$ is a group of formula (i) or (ii), n is preferably 2 or 3.

Preferably $R^5$ is a group (ii), most preferably a group (ii) in which the N-linked heterocycle is an unsubstituted piperidine or morpholine ring.

When $R^5$ is a group (i), $R^6$ and $R^7$ may be $C_{1-6}$alkyl or aryl$C_{1-6}$alkyl, each of which is optionally substituted by one or more of, for example, $C_{1-6}$alkoxy, cyano, hydroxy and heterocycles such as dioxolanyl.

Preferably ------- represents a single bond and both X and Y are $CH_2$.

Particularly preferred compounds of this invention include:

(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]propenone hydrochloride;
(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-morpholin-4-ylethoxy)-2,3-dihydro-indol-1-yl]propenone;
(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-ylethoxy)-2,3-dihydroindol-1-yl]propenone;
(E)-3-(2-Chloro-phenyl)-1-{5-methoxy-6-[2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone;
(E)-1-{6-[2-(tert-Butyl-methyl-amino)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-3-(2-chloro-phenyl)-propenone;
(E)-3-(2-Chloro-phenyl)-1-[6-(2-diethylamino-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-propenone;
(E)-3-(2-Chloro-phenyl)-1-[6-(2-dimethylamino-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-propenone;

or a pharmaceutically acceptable salt thereof.

Other preferred compounds of this invention include compounds, shown in Tables 1, 2, 3, 4 and in the Examples below, or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can form acid addition salts. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric,

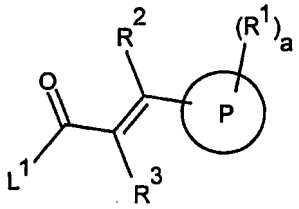
hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid.

The compounds of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. geometric or ("*cis-trans*") isomers, diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

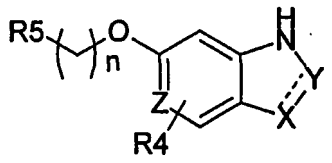
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises either:

(a) the coupling of a compound of formula (II):




(II)

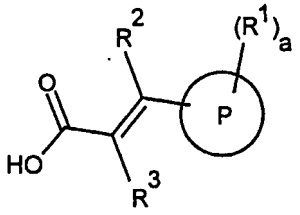
in which $R^1$, $R^2$, $R^3$, P and a are as defined in formula (I) and $L^1$ is a leaving atom with a compound of formula (III):



(III)

in which X, Y, ------, $R^4$, $R^5$, Z and n are as defined in formula (I); or

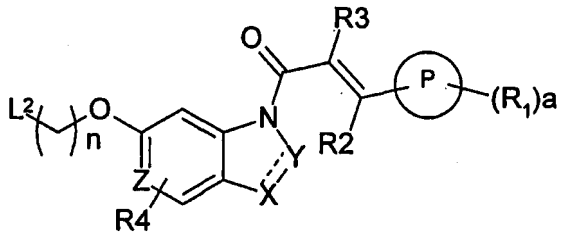
(b) the coupling of a compound of formula (IV)



(IV)

in which $R^1$, $R^2$, $R^3$, P and a are as defined in formula (I) with a compound of formula (III) as defined in process (a) in the presence of suitable amide coupling reagent; or

(c) when $R^5$ is a group (i) or (ii), the coupling of a compound of formula (V)



(V)

in which X, Y, ------, $R^1$, $R^2$, $R^3$, $R^4$, Z, P, a and n are as defined in formula (I) and $L^2$ is a leaving group, with a compound of formula (VI)

H - $NR^6R^7$ or H - (N-linked heterocycle)

(VI)

in which N-linked heterocycle, $R^6$ and $R^7$ are as defined in formula (I);
and optionally thereafter for either process (a),(b) or (c)

- removing any protecting groups; and/or
- converting a compound of formula (I) into another compound of formula (I); and/or
- forming a pharmaceutically acceptable salt.

For process (a) suitable leaving atoms $L^1$ are halogen, in particular chloro. The reaction of a compounds of formulae (II) and (III) is preferably carried out in an inert solvent such as dichloromethane optionally in the presence of a base such as triethylamine or pyridine.

For process (b) suitable amide coupling reagents include those which are well known to those skilled in the art and include reagents such as 1,3-dicyclohexylcarbodiimide (DCC), O-benzotriazol-1-yl-N,N,N',N'-tetramethyl-uroniumhexafluorophosphate (HBTU) or O-benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP).

For process (c) suitable leaving groups $L^2$ include halogen, mesylate or tosylate. The reaction of a compound of formulae (V) and (VI) is preferably carried out in an inert solvent such as dimethylformamide, optionally in the presence of sodium iodide and a base such as potassium carbonate.

Those skilled in the art will appreciate that it may be necessary to protect certain groups to carry out the above processes. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

Compounds of formulae (II) - (VI) are either commercially available, may be prepared according to methods described herein or by may be prepared according to known methods or by analogous methods thereto.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have 5-$HT_{2C}$ receptor antagonist activity and are of use for the treatment or prophylaxis of CNS disorders such as anxiety, depression (both bipolar and unipolar), single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, dysthymic disorder with early or late onset and with or without atypical features, neurotic depression, post traumatic stress disorder, social phobia, vascular dementia with depressed mood, mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances, schizoaffective disorder of the depressed type, adjustment disorder with depressed mood, epilepsy, obsessive compulsive disorders, migraine, Alzheimer's disease with early or late onset and/or with depressed mood; cognitive disorders including dementia, amnestic disorders and cognitive disorders not otherwise specified, sleep disorders (including disturbances of Circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), feeding disorders such as anorexia, anorexia nervosa and bulimia, panic attacks, withdrawal from drug abuse such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. cannabis, heroin, morphine), sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) or a combination thereof, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Depressive disorders which may be treated or prevented by the compounds of formula (I) and their pharmaceutically acceptable salts may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, *etc.* Furthermore compounds of the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

In particular, the compounds of the present invention are useful for the treatment and/or prophylaxis of depression and/or anxiety.

Compounds of the invention may be administered in combination with other active substances such as 5HT3 antagonists, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

Compounds of the invention are also of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

Thus the invention also provides for a compound of formula (I) or a pharmaceutically acceptable salt or a solvate thereof for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof for use in the treatment or prophylaxis of CNS disorders, particularly depression, anxiety, schizophrenia and/or sleep disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to a patient in need thereof a safe and therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of the above disorders, particularly CNS disorders including depression and/or anxiety.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient. A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); wetting agents (e.g. sodium lauryl sulphate) or tabletting lubricants. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents

(e.g. lecithin or acacia), non-aqueous vehicles (which may include edible oils e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid), and, if desired, the preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose, utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle, optionally with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device. Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three times a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

**Description 1**

**l-[2-(2-Methoxy-5-nitro-phenoxy)ethyl]piperidine (D1)**

2-Methoxy-5-nitrophenol (25 g) and 1-(2-chloroethyl)piperidine hydrochloride (27.2 g) were added to a mixture of saturated aqueous potassium carbonate (200 ml), water (300 ml) and 1,2-dimethoxyethane (800 ml). The reaction mixture was refluxed for 5 h, after which it was cooled and diluted with ethyl acetate (800 ml), then washed with water (2x 200 ml) and brine (200 ml). The organics were then extracted with 1M aqueous hydrochloric acid (2x 200 ml). The aqueous was then carefully basified to pH 13 with potassium carbonate. The resulting solution was extracted with DCM (500 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (D1) as a white solid (27.2 g, 70%). MS m/z ($MH^+$) 281.

**Description 2**

**1-[2-(2-Methoxy-5-nitro-phenoxy)-ethyl]-pyrrolidine (D2)**

The title compound (D2) was prepared from 2-methoxy-5-nitrophenol and 1-(2-chloro-ethyl)-pyrrolidine according to the procedure described for the preparation of D1. MS m/z ($MH^+$) 267.

**Description 3**

**4-[2-(2-Methoxy-5-nitro-phenoxy)-ethyl]-morpholine (D3)**

The title compound (D3) was prepared from 2-methoxy-5-nitrophenol and 1-(2-chloro-ethyl)-morpholine according to the procedure described for the preparation of D1. MS m/z ($MH^+$) 283.

**Description 4**

**4-Methoxy-3-(2-piperidin-1-ylethoxy)phenylamine (D4)**

1-[2-(2-Methoxy-5-nitrophenoxy)ethyl]piperidine (D1) (27.3 g) was taken up in ethanol (500 ml) and 10% Pd/C (7 g) was then added to the solution. The mixture was hydrogenated at atmospheric pressure for 12 h at room temperature and then filtered through Celite (diatomaceous earth). Concentration of the filtrate gave the title compound (D4) as a red oil (25.2 g, 100%). MS m/z ($MH^+$) 251.

**Description 5**

**4-Methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (D5)**

The title compound (D5) was prepared from 1-[2-(2-methoxy-5-nitro-phenoxy)-ethyl]-pyrrolidine (D2) according to the procedure described for the preparation of D4. MS m/z ($MH^+$) 237.

**Description 6**

**4-Methoxy-3-(2-morpholin-4-yl-ethoxy)-phenylamine (D6)**

A mixture of 4-[2-(2-methoxy-5-nitro-phenoxy)-ethyl]-morpholine (D3)(12.4g, 44 mmol), iron powder (7.0g) in saturated aqueous ammonium chloride (200 mL) and methanol (200 mL) was heated to 110°C for 4 h. The mixture was allowed to cool to room temperature and solid residues filtered off. The organic layer was separated and the aqueous was further extracted with dichloromethane (2 x 100 mL). The combined organics were evaporated and residual water azeotropically removed with toluene (50 mL) to afford the title compound (D6)(10.6 g, 96%). MS m/z ($MH^+$) 253.

**Description 7**

**(2,2-Dimethoxyethyl)-[4-methoxy-3-(2-piperidin-1-ylethoxy)phenyl]amine (D7)**

To a mixture of 4-methoxy-3-(2-piperidin-1-ylethoxy)phenylamine (D4) (1 g) and glyoxal 1,1-dimethylacetal solution (~ 45% in *tert*-butylmethylether, 1.66 g) in ethanol (30 ml) was added 10% Pd/C (200 mg) and the reaction mixture was then stirred under an atmosphere of hydrogen at room temperature for 10 h. After filtration through Celite (diatomaceous earth) the filtrate was concentrated *in vacuo* to leave a red oil which was dissolved in ethyl acetate (100 ml) and washed with water (2 x 25 ml). The organic phase was then dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (D7) as a brown oil (1.4 g, 88%). MS m/z ($MH^+$) 339.

**Description 8**

**(2,2-Dimethoxy-ethyl)-[4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine (D8)**

The title compound (D8) was prepared from 4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (D5) according to the procedure described for the preparation of D7. MS m/z ($MH^+$) 325.

**Description 9**

**(2,2-Dimethoxy-ethyl)-[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-amine (D9)**

A solution of 4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenylamine (D6) (10g, 39.7 mmol) and glyoxal 1,1-dimethylacetal solution (~ 40% solution in water) (5mL, 43.6 mmol) in methanol (100 mL) and acetic acid (10 mL) was treated with sodium cyanoborohydride (1.7g) over a period of 30 mins. A further amount of glyoxal 1,1-dimethylacetal solution (~ 40% solution in water) (5mL, 43.6 mmol) was added followed by sodium cyanoborohydride (1.7g) added over 30 minutes. Toluene (30 mL) was added and the reaction mixture reduced to a small volume. The residue was diluted with water (100 mL), basified with 5N NaOH and the product extracted with ether (10 x 60 mL) and dichloromethane (2 x 50 mL). The combined organics were evaporated to afford the title compound (D9)(11.6g, 86%). MS m/z ($MH^+$) 341.

**Description 10**

**5-Methoxy-6-(2-piperidin-1-ylethoxy)-1*H*-indole (D10)**

A solution of (2,2-dimethoxyethyl)-[4-methoxy-3-(2-piperidin-1-ylethoxy)-phenyl]amine (D7) (1.4 g), in trifluoroacetic acid (6 ml) at 0°C under argon was treated with trifluoroacetic anhydride (9 ml) dropwise over 40 minutes. The reaction mixture was then warmed to room temperature over 30 min. and then refluxed for 7 h. The cooled mixture was concentrated *in vacuo* and 10% aqueous sodium carbonate solution (50 ml) was added to the residue. The resultant mixture was extracted with ethyl acetate (3 x 50 ml) and the combined extracts were dried ($MgSO_4$) and concentrated to a residue. The residue was dissolved in methanol (20 ml) and stirred with potassium carbonate (2 g) at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* and water (30 ml) was added to the residue. The resultant mixture was extracted with ethyl acetate (3 x 25 ml). The combined organics were dried ($MgSO_4$) and concentrated to give the title compound (D10) as a brown oil (0.80 g, 73%). MS m/z ($MH^+$) 275.

**Description 11**

**5-Methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-1H-indole (D11)**

The title compound (D11)was prepared from (2,2-dimethoxy-ethyl)-[4-methoxy-3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine (D8) according to the procedure described for the preparation of D10. MS m/z ($MH^+$) 261.

**Description 12**

**5-Methoxy-6-(2-morpholin-4-yl-ethoxy)-1H-indole (D12)**

The title compound (D12) was prepared from (2,2-dimethoxy-ethyl)-[4-methoxy-3-(2-morpholin-4-yl-ethoxy)-phenyl]-amine (D9) according to the procedure described for the preparation of D10. MS m/z ($MH^+$) 277.

**Description 13**

**5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydro-1*H*-indole (D13)**

A solution of 5-methoxy-6-(2-piperdin-1-ylethoxy)-1*H*-indole (D10) (0.50 g) in acetic acid (10 ml) was treated with sodium cyanoborohydride (0.25 g) portion-wise over 20 min. The reaction mixture was stirred for 2 h at room temperature, and then diluted with water (10 ml) and basified with sodium carbonate. The resulting mixture was extracted with ethyl acetate (3 x 100 ml) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (D13) as a brown oil (0.36 g, 72%). MS m/z ($MH^+$) 277.

**Description 14**

**5-Methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-1H-indole (D14)**

The title compound (D14) was prepared from 5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-1H-indole (D11) according to the procedure described for the preparation of D13. MS m/z ($MH^+$) 263.

**Description 15**

**5-Methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-1H-indole (D15)**

The title compound (D15) was prepared from 5-methoxy-6-(2-morpholin-4-yl-ethoxy)-1H-indole (D12) according to the procedure described for the preparation of D13. MS m/z ($MH^+$) 279.

**Description 16**

**(*E*)-3-(2-Trifluoromethoxyphenyl)acrylic acid ethyl ester (D16)**

A mixture of 2-trifluoromethoxybenzaldehyde (25 g), potassium carbonate (36.5 g), triethylphosphonoacetate (29.5 g) in water (30 ml) was heated to 70°C for 4 h. The

mixture was then filtered to remove the solid residue which was washed with water (10 ml). The combined filtrates were extracted with ether (5 x 50 ml). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (D16) as a colourless oil ( 29.2 g, 85%). MS m/z ($MH^+$ 261).

**Description 17**

**(*E*)-3-(2-Trifluoromethoxyphenyl)acrylic acid (D17)**

A solution of (*E*)-3-(2-trifluoromethoxyphenyl)acrylic acid ethyl ester (D16) (2.0 g) in ethanol (300 ml) was treated with sodium hydroxide (9.0 g) in water (50 ml) and the resultant solution was refluxed for 2 h. After cooling the mixture was concentrated *in vacuo* and the residue was treated with water (200 ml) and acidified with concentrated hydrochloric acid to pH 1. The resultant precipitate was removed by filtration and the filtrate was extracted with ethyl acetate (3 x 100 ml). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (D17) as a pale yellow solid (22.86 g, 88%). MS m/z ($MH^-$ 231).

**Description 18**

**2-[1-Hydroxy-1-(2-trifluoromethoxyphenyl)methyl]acrylic acid *tert*-butyl ester (D18)**

A mixture of 2-trifluoromethoxybenzaldehyde (25 g), 1,4-diazabicyclo[2,2,2]-octane (3 g) in *tert*-butylacrylate (38 ml) was stirred until a homogeneous solution, it was then left to stand at room temperature for 14 days. The mixture was then diluted with ethyl acetate (300 ml), washed with 1N hydrochloric acid (100 ml), water (100 ml) and brine (100 ml). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (D18) as a colourless oil (36 g, 100%).

$^1H$ (250 MHz, $CDCl_3$) δ 1.42 (9H, s), 5.62 (1H, s), 5.86 (1H, s), 6.26 (1H, s), 6.03 (1H, s), 7.33 (4H, m).

**Description 19**

**2-[1-Acetoxy-1-(2-trifluoromethoxyphenyl)methyl]acrylic acid *tert*-butyl ester (D19)**

A solution of 2-[1-hydroxy-1-(2-trifluoromethoxyphenyl)methyl]acrylic acid *tert*-butyl ester (D18) (36 g) and pyridine (23 ml) in DCM (200 ml) was stirred together and the solution was treated dropwise with acetyl chloride (18.1 ml). After 1 h the solution was washed with 1N hydrochloric acid (100 ml) and brine (100 ml) dried ($MgSO_4$) and concentrated *in vacuo* to leave the title compound (D19) as a yellow oil (40 g, 96%).

$^1$H (250 MHz, $CDCl_3$) δ 1.36 (9H, s), 2.10 (3H, s), 5.64 (1H, s), 6.39 (1H, s), 7.37 (4H, m).

**Description 20**

**(*E*)-3-(2-Trifluoromethoxyphenyl)-2-methylacrylic acid *tert*-butyl ester (D20)**

A solution of 2-[1-acetoxy-1-(2-trifluoromethoxyphenyl)methyl]acrylic acid *tert*-butyl ester (D19) (40 g) was dissolved in *tert*-butanol (500 ml) and treated portion wise with sodium borohydride (4.2 g) over 0.5 h. The reaction mixture was stirred at room temperature for 12 h then concentrated *in vacuo* to give a residue which was dissolved in ethyl acetate (200 ml) and washed with water (150 ml) then brine (100 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (D20) as a yellow oil (30 g, 89%).

$^1$H (250 MHz, $CDCl_3$) δ 1.55 (9H, s), 1.95 (3H, s), 7.33 (4H, m), 7.63 (1H, s).

**Description 21**

**(*E*)-3-(2-Trifluoromethoxyphenyl)-2-methylacrylic acid (D21)**

A solution of (*E*)-3-(2-trifluoromethoxyphenyl)-2-methylacrylic acid *tert*-butyl ester (D20) (30 g) in DCM (200 ml) was treated with trifluoroacetic acid (200 ml) and left to stand at room temperature for 3 h. The reaction mixture was then concentrated *in vacuo* to give the title compound (D21) (23.2 g, 95%).

$^1$H (250 MHz, $CDCl_3$) δ 2.03 (3H, s), 7.42 (4H, m), 7.88 (1H, s).

**Description 22**

**2-(Diethoxy-phosphoryl)-propionic acid (D22)**

Triethyl-2-phosphonopropionate (50g, 0.21 mol) was dissolved in methanol (200 mL) and saturated aqueous KOH was added portionwise at 0°C. The reaction was allowed to warm to room temperature and stirring was continued for 18 h. After removal of methanol *in vacuo*, the residue was acidified with HCl to pH1 and extracted with dichloromethane (2 x 100 mL). The combined organics were washed with brine, dried (MgSO4) and evaporated *in vacuo* to afford the title compound (D22)(36g, 82%).

**Description 23**

**(E)-3-(2,3-Dichloro-phenyl)-2-methyl-acrylic acid (D23)**

A solution of 2-(diethoxy-phosphoryl)-propionic acid (D22) (0.5g, 2.4mmol) in THF (2.5 mL) was added dropwise to a solution of butyllithium(1.6M in hexanes, 3.1 mL, 5 mmol) in THF (8 mL) at –60°C. Stirring was continued at –60°C for 30 minutes before 2,3 dichlorobenzaldehyde (0.42 g, 2.4 mmol) was added as a solution in THF

(1.2 mL). After an additional 60 minutes at –60°C, the reaction was allowed to warm to room temperature over 3 h. The mixture was hydrolysed with water (6 mL) and separated. The organic phase was washed with 10% aqueous sodium bicarbonate solution (2 x 5mL) and the combined aqueous phases washed with ether (2 x 6 mL). The aqueous phase was acidified with 5N HCl to pH1 and the resulting precipitate filtered off, washed with water and dried to afford the title compound as a white solid 0.44g, 80%). MS m/z ($MH^+$ 231/233/235).

**Description 24**

**(E)-2-Methyl-3-(2,3,6-trichloro-phenyl)-acrylic acid (D24)**

The title compound was prepared from 2-(diethoxy-phosphoryl)-propionic acid (D22) and 2,3,6 trichlorobenzaldehyde according to the procedure described for the preparation of D23. MS m/z ($MH^+$ 265/267/269/271).

**Description 25**

**(E)-3-(2,6-Difluoro-phenyl)-2-methyl-acrylic acid (D25)**

The title compound was prepared from 2-(diethoxy-phosphoryl)-propionic acid (D22) and 2,6 difluorobenzaldehyde according to the procedure described for the preparation of D23. MS m/z ($MH^+$ 199).

**Description 26**

**(E)-3-(4-Fluoro-phenyl)-2-methyl-acrylic acid (D26)**

The title compound was prepared from 2-(diethoxy-phosphoryl)-propionic acid (D22) and 4-fluorobenzaldehyde according to the procedure described for the preparation of D23. MS m/z ($MH^+$ 181).

**Description 27**

**(E)-3-(2-Chloro-3,6-difluoro-phenyl)-2-methyl-acrylic acid (D27)**

The title compound was prepared from 2-(diethoxy-phosphoryl)-propionic acid (D22) and 2-chloro-3,6- difluorobenzaldehyde according to the procedure described for the preparation of D23. MS m/z ($MH^+$ 233/235).

**Description 28**

**(E)-2-Methyl-3-(2,3,5-trifluoro-phenyl)-acrylic acid (D28)**

The title compound was prepared from 2-(diethoxy-phosphoryl)-propionic acid (D22) and 2,3,5 trifluorobenzaldehyde according to the procedure described for the preparation of D23. MS m/z ($MH^+$ 217).

**Description 29**

**(E)-3-(2-Bromo-phenyl)-2-methyl-acrylic (D29)**

The title compound was prepared from 2-(diethoxy-phosphoryl)-propionic acid (D22) and 2-bromobenzaldehyde according to the procedure described for the preparation of D23. MS m/z ($MH^+$ 241/243).

**Description 30**

**2-(2-Benzyloxyethoxy)-1-methoxy-4-nitrobenzene (D30)**

A mixture of 2-methoxy-5-nitrophenol (12.9 g , 76.3 mmol), anhydrous potassium carbonate (13.9 g, 100.5 mmol), benzyl-2-bromoethyl ether (20 g, 93 mmol) and sodium iodide (1.47 g, 9.8 mmol) in dry DMF (100 ml) was stirred under argon at 60°C for 27 h. The solvent was removed and the residue was treated with DCM (300 ml). The solid was filtered-off and washed with DCM (2 x 50 ml). The combined filtrate and washings were evaporated and the residue was co-evaporated with toluene (2 x 20 ml). The resulting oil was triturated with hexane (2 x 100 ml) and co-evaporated with toluene (1 x 20 ml) to give the title compound (D30) as a yellow viscous oil (23 g, 99%).

$^1H$ (250 MHz, $CDCl_3$) δ 3.93 (2H, m), 3.96 (3H, m), 4.28 (2H, m), 4.65 (3H, s), 6.90 (1H, d, *J* 7.5 Hz), 7.31 (5H, m), 7.80 (1H, d, *J* 2.5 Hz), 7.92 (1H, dd, *J* 7.5 Hz).

**Description 31**

**3-(2-Benzyloxyethoxy)-4-methoxyphenylamine (D31)**

2-(2-Benzyloxyethoxy)-1-methoxy-4-nitrobenzene (D30) (23 g, 75.6 mmol) and iron (12.8 g) in saturated aqueous ammonium chloride/methanol solution (1:1, 500 ml) was heated at 120°C for 3.5 h. After cooling to room temperature the solid was removed by filtration through Celite (diatomaceous earth) and washed with methanol (50 ml) and DCM (500 ml). The filtrate and washings were combined and the layers separated. The aqueous layer was extracted with DCM (1 x 100 ml). The combined organic phases were washed with water (1 x 200 ml) dried ($MgSO_4$) and evaporated. The residue was co-evaporated with toluene (2 x 50 ml) to give the title compound (D31) as a tan solid (21.1 g, 82%). MS: m/z ($MH^+$) 274/275.

**Description 32**

**[3-(2-Benzyloxyethoxy)-4-methoxyphenyl]-(2,2-dimethoxyethyl)amine (D32)**

Sodium cyanoborohydride (7.4 g, 117.2 mmol) was added in portions during 45 min. to a solution of 3-(2-benzyloxyethoxy)-4-methoxyphenylamine (D31) (8.0 g 29.3 mmol), glyoxal 1,1-dimethyl acetal (45% solution in tert-butyl methyl ether; 4.6 g)

and glacial acetic acid (5.0 ml) in methanol (150 ml) under argon at room temperature. A further amount of glyoxal 1,1-dimethyl acetal (45% solution in tert-butyl methyl ether; 4.5 g) was added 20 minutes before the above addition of sodium cyanoborohydride was complete. The reaction mixture was stirred for another 1 h at room temperature and then diluted with benzene (100 ml). The solvents were evaporated to a small volume, the residue was treated with ice (50 ml) and basified with saturated aqueous sodium carbonate. The product was extracted with diethyl ether (5 x 50 ml), the combined extracts were dried ($MgSO_4$) and evaporated to give the title compound (D32) as a tan gum (10.6 g). MS: m/z ($MH^+$) = 362/363.

**Description 33**

**6-(2-Benzyloxyethoxy)-5-methoxyindole-1-carboxylic acid trifluoromethyl ester (D33)**

Trifluoroacetic anhydride (5.7 ml, 40 mmol) was added dropwise to an ice cooled, stirred solution of [3-(2-benzyloxy-ethoxy)-4-methoxyphenyl]-(2,2-dimethoxy-ethyl)amine (D32) (10.6 g, 29.3 mmol) and triethylamine (4.3 g, 43 mmol) in DCM/hexane (3:2, 250 ml). After 10 min. at 0°C then 2 h at room temperature DCM (50 ml) was added. The mixture was washed with water (2 x 70 ml), saturated aqueous sodium bicarbonate (2 x 70 ml), water (2 x 70 ml) and dried ($MgSO_4$). The solvents were removed and the residue was co-evaporated with toluene (2 x 50 ml) to give a tan gum. The gum was dissolved in a 33% (v/v) solution of trifluoroacetic anhydride in trifluoroacetic acid (300 ml) and the solution was heated at 60°C under argon for 2 h 10 min. The solvents were evaporated, the residue was co-evaporated with toluene (1 x 50 ml) and the product was purified by column chromatography on silica gel (eluting with ethyl acetate-hexane gradient ) to give the title compound (D33) as a slightly blue solid (5.59 g, 48%). MS: m/z ($MH^+$) = 394/395.

**Description 34**

**6-(2-Benzyloxyethoxy)-5-methoxy-1*H*-indole (D34)**

A mixture of 6-(2-benzyloxyethoxy)-5-methoxyindole-1-carboxylic acid trifluoromethyl ester (D33) (4.9 g, 12.45 mmol) and anhydrous potassium carbonate (3.5 g, 25 mmol) in methanol (100 ml) was stirred at room temperature for 25 min. The solvent was removed, water (100 ml) was added and the product was extracted with ethyl acetate (4 x 50 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give the title compound (D34) as a tan solid (3.68 g, 99%). MS: m/z ($MH^+$) = 298/299.

**Description 35**

**6-(2-Benzyloxyethoxy)-5-methoxy-2,3-dihydro-1*H*-indole (D35)**

Sodium cyanoborohydride (2.4 g, 38.1 mmol) was added in portions during 20 min to a stirred solution of 6-(2-benzyloxyethoxy)-5-methoxy-1*H*-indole (D34) (3.66 g, 12.32 mmol) in glacial acetic acid (100 ml) under argon at room temperature. After 2.5 h, toluene (100 ml) was added, the solvents were evaporated to a small volume and the residue was treated with ice (100 ml). The solution was basified with solid sodium carbonate and extracted with ethyl acetate (3 x 100 ml). The combined organics were dried ($MgSO_4$) and evaporated and the residue was co-evaporated with toluene (2 x 30 ml) to give the title compound (D35) as a tan gum (3.7 g, 99%). MS: m/z ($MH^+$) = 300/301.

**Description 36**

**2-(5-Methoxy-2,3-dihydro-1*H*-indole-6-yloxy)ethanol hydrochloride salt (D36)**

A mixture of 6-(2-benzyloxyethoxy)-5-methoxy-2,3-dihydro-1*H*-indole (D35) (3.67 g, 12.27 mmol), 10% palladium on carbon (1.0 g) and acetic acid (1 ml) in ethanol (150 ml) was stirred under hydrogen (50 psi, 344.8KPa) at room temperature. After 17 h, hydrochloric acid (37%) (1 ml) was added, followed by another addition of hydrochloric acid (37%) (1 ml) after 5 h. The stirring under hydrogen was then continued for a further 17 h. The catalyst was filtered off and washed with ethanol (300 ml), the filtrate and washings were then combined and evaporated. The residue was co-evaporated with methanol-toluene mixture (3 x 20 ml) and with toluene (1 x 20 ml) to give the title compound (D36) as a dark green solid (3.1 g, 99%). MS: m/z ($MH^+$) = 210/211.

**Description 37**

**(*E*)-3-(2-Chlorophenyl)-1-[6-(2-hydroxyethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]propenone (D37)**

A solution of 2-chlorocinnamoyl chloride (2.5 g, 12.43 mmol) in DCM (10 ml) was added dropwise during 2 h to a stirred solution of 2-(5-methoxy-2,3-dihydro-1*H*-indole-6-yloxy)ethanol hydrochloride (D36) (3.1 g, 12.3 mmol) in DCM-pyridine (5:1, 60 ml) under argon at 0°C. After a further 15 minutes at 0°C, DCM (100 ml) was added and the mixture was washed with saturated aqueous sodium bicarbonate (2 x 20 ml) and dried ($MgSO_4$). The solvents were evaporated, the residue was co-evaporated with toluene (2 x 10 ml) and the product was purified by column chromatography on silica gel (eluting with ethyl acetate–DCM and then with methanol-DCM gradient) to give the title compound (D37) as a yellow solid (3.0 g, 64%). MS: m/z ($MH^+$) = 374/376.

**Description 38**

**Methanesulfonic acid 2-{1-[(*E*)-3-(2-chlorophenyl)allanoyl]-5-methoxy-2,3-dihydro-1*H*-indol-6-yloxy}-ethyl ester (D38)**

A mixture of (*E*)-3-(2-chlorophenyl)-1-[6-(2-hydroxyethoxy)-5-methoxy-2,3-dihydroindol-1-yl]propenone (D37) (3.0 g, 8.02 mmol), methanesulphonyl chloride (1.8 g, 15.7 mmol) and triethylamine (1.9 g, 19 mmol) in DCM (100 ml) was stirred at room temperature for 3 h. DCM (50 ml) was added and the solution was washed with saturated aqueous sodium bicarbonate (3 x 20 ml), water (1 x 20 ml) and dried ($MgSO_4$). The solvents were removed and the residue was co-evaporated with toluene (2 x 10 ml) to give the title compound (D38) as a yellow glass (3.61 g, >99%). $^1H$ (250 MHz, $CDCl_3$) δ 3.19 (5 H, m), 3.82 (3 H, s), 4.3 (4 H, m), 4.61 (2 H, m), 6.77 (1 H, s), 6.84 (1 H, d, *J* 15.4 Hz), 7.29 (2 H, m), 7.42 (1 H, m), 7.62 (1 H, m), 8.14 (1 H, m), 8.18 (1 H, d, *J* 15.4 Hz).

**Description 39**

**(E)-3-(2,4-Dichloro-phenyl)-1-[6-(2-hydroxy-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-propenone (D39)**

The title compound D39 was prepared from D36 and 2,4 dichlorocinnamoyl chloride according to the procedure described for the preparation of D37. MS: m/z ($MH^+$) = 408/410/412.

**Description 40**

**Methanesulfonic acid 2-{1-[(E)-3-(2,4-dichloro-phenyl)-allanoyl]-5-methoxy-2,3-dihydro-1H-indol-6-yloxy}-ethyl ester (D40)**

The title compound D40 was prepared from D39 using the procedure described for the preparation of D38. MS: m/z ($MH^+$) = 486/488/490.

**Description 41**

**(*E*)-1-[6-(2-Hydroxyethoxy)-5-methoxy-2,3-dihydroindol-1-yl]-3-(2-trifluoromethoxy-phenyl)-propenone (D41)**

A mixture of (*E*)-3-(2-trifluoromethoxyphenyl)acrylic acid (D17) (1.86 g, 8 mmol,), isobutyl chloroformate (1.1 g, 8 mmol), and 4-methylmorpholine (0.8 g, 8 mmol) in THF (50 ml) was stirred at 0°C for 10 min. 2-(5-Methoxy-2,3-dihydro-1*H*-indole-6-yloxy)ethanol hydrochloride (D36) (1.72 g, 7 mmol) in DMF (10 ml) and triethylamine (1.2 g, 12 mmol) were added and the mixture was stirred at room temperature for 17 h. The solvents were evaporated, the residue was dissolved in DCM (50 ml), washed with 6N aqueous citric acid (2 x 20 ml), saturated aqueous

sodium bicarbonate (2 x 10 ml), water (1 x10 ml) and dried ($MgSO_4$). The solvent was evaporated, the product was purified by column chromatography on silica gel (eluting with DCM-ethyl acetate gradient and then with DCM-methanol gradient) to give the title compound (D41) as a yellow solid (1.0g 34%).

$^1H$ (250 MHz, $CDCl_3$) δ 2.54, (1H, t, *J* 6.41 Hz), 3.21 (2H, t, *J* 8.35 Hz), 3.85 (3 H, s), 3.92 (2 H, m,), 4.20 (2 H, t, *J* 4.5 Hz), 4.29 (1 H, t, *J* 8.35 Hz), 6.78 (1 H, s), 6.94 (1 H, d, *J* 15.5 Hz), 7.38 (3 H, m), 7.65, (1H, d, m), 7.98 (1 H, d, *J* 15.5 Hz), 8.16 (1 H, s); MS: m/z ($MH^+$) = 424/425.

**Description 42**

**Methanesulfonic acid 2-{5-methoxy-1-[(*E*)-3-(2-trifluoromethoxyphenyl)-allanoyl]-2,3-dihydro-1*H*-indol-6-yloxy}-ethyl ester (D42)**

The title compound (D42) was prepared from (*E*)-1-[6-(2-hydroxyethoxy)-5-methoxy-2,3-dihydroindol-1-yl]-3-(2-trifluoromethoxy-phenyl)propenone (D41) according to the procedure described for preparation of D38. $^1H$ (250 MHz, $CDCl_3$) δ 3.17 (5 H, m), 3.82 (3 H, s), 4.31 (4 H, m), 4.60 (2 H, m), 6.78 (1 H, s), 6.94 (1 H, d, *J* 15.5 Hz), 7.36 (3 H, m), 7.66 (1 H, d, *J* 7.6 Hz), 7.97 (1 H, d, *J* 15.5 Hz), 8.13 (1H, s).

**Description 43**

***tert*-Butyl-[2-(2-methoxy-5-nitrophenoxy)ethoxy]dimethylsilane (D43)**

2-Methoxy-5-nitrophenol (17.7 g),was dissolved in DMF (100 ml) and treated with potassium carbonate (18.8 g), sodium iodide (1.88 g) and 2-(bromoethoxy)-*tert*-butyl-dimethylsilane (30.0 g). The mixture was heated at 76°C for 24 h under argon and allowed to cool to room temperature. The mixture was concentrated *in vacuo* and the residue azeotroped with toluene. The residue was dissolved in DCM (500 ml) and the inorganics removed by filtration. The organics were washed with water (200ml x 3), dried ($MgSO_4$) and concentrated *in vacuo*. The crude compound was triturated with hexane (150 ml) and a small amount of a precipitated light brown solid was filtered off and washed with hexane. This was identified as 2-(2-methoxy-5-nitrophenoxy)ethanol (1.9 g, D44). The mother liquors were concentrated *in vacuo* to give the title compound (D43) as a brown solid (31.6 g, 92%).

$^1H$ (400 MHz, $CDCl_3$) δ 0.01(6H, s), 0.80 (9H, s), 3.86 (3H, s), 3.94 (2H, t, J 5.2 Hz ), 4.09 (2H, t, J 5.2 Hz), 6.81 (1H, d, J 8.8 Hz), 7.72 (1H, d, J 2.8 Hz), 7.81 (1H, dd, J 2.8 Hz, 9.2 Hz).

**Description 44**

**2-(2-Methoxy-5-nitrophenoxy)ethanol (D44)**

*tert*-Butyl-[2-(2-methoxy-5-nitrophenoxy)ethoxy]dimethylsilane (D43) (67 g) was dissolved in THF (70 ml), treated with tetrabutylammonium fluoride (1.0 M solution in THF, 410 ml) and the mixture stirred at room temperature for 3 h under argon. The mixture was concentrated *in vacuo* and the residue partitioned between DCM (900 ml) and water (400 ml). The organic layer was separated, washed with water( 400 ml x 3), brine (400 ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The solid was triturated with hexane and filtered off. The solid was washed with further hexane (100 ml x 3) to give the title compound (D44) as a beige solid (34.5 g, 79%). The mother liquors were concentrated *in vacuo* and the residue triturated with hexane. The solid was filtered off and washed with hexane(25 ml x 3) to give a second batch of title compound as a beige solid (2.3 g, 5%).

$^1H$ (400 MHz, $CDCl_3$) δ 2.45 (1H, br s), 3.97 (3H, s), 4.03, (2H, br s), 4.20 (2H, m), 6.93 (1H, d, J 9.0 Hz), 7.78 (1H, d, J 2.6 Hz), 7.94 (1H, dd, J 2.6 Hz, 9.0 Hz).

**Description 45**

**Methanesulfonic acid 2-(2-methoxy-5-nitrophenoxy) ethyl ester (D45)**

2-(2-Methoxy-5-nitro-phenoxy)ethanol (D44) (18.75 g) was dissolved in DCM (150ml) and treated with triethylamine (20.9 ml). The mixture was cooled in an ice-water bath and methane sulphonyl chloride (10.2 ml) slowly added. The mixture was allowed to warm to room temperature and was stirred for 1.5 h under argon. The mixture was diluted with DCM (450 ml) and washed with saturated sodium bicarbonate solution (250 ml x 4), water (250 ml x 3) and brine (150 ml). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to give the title product (D45) as a yellow/brown solid (23.8 g, 93%).

$^1H$ (400 MHz, $CDCl_3$) δ 3.15 (3H, s), 3.96 (3H, s), 4.35 (2H, m), 4.64 (2H, m), 6.96 (1H, d, J 9.0 Hz), 7.77 (1H, d, J 2.6 Hz), 7.97(1H, dd, J 2.6 Hz, 8.9 Hz).

**Description 46**

**4-[2-(2-Methoxy-5-nitrophenoxy)ethyl]piperazine-1-carboxylic acid *tert*-butyl ester (D46)**

Methanesulfonic acid 2-(2-methoxy-5-nitrophenoxy) ethyl ester (D45) (23.8 g) was dissolved in DMF (300 ml) and treated with potassium carbonate (22.6 g), sodium iodide (12.0 g) and *tert*-butyl-1-piperazine carboxylate (18.3 g). The mixture was heated at 62°C for 24 h under argon. The mixture was concentrated *in vacuo* and the residue dissolved in ethyl acetate (550 ml) and washed with water (750 ml and 300 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude compound was purified by column chromatography on silica gel eluting initially with DCM then

in a gradient of ethyl acetate in DCM to neat ethyl acetate to give the title compound (D46) as a yellow/brown solid (24.7 g, 79%), MS: m/z ($MH^+$) 382.

**Description 47**

**4-[2-(5-Amino-2-methoxyphenoxy)ethyl]piperazine-1-carboxylic acid *tert*-butyl ester (D47)**

4-[2-(2-Methoxy-5-nitrophenoxy)ethyl]piperazine-1-carboxylic acid *tert*-butyl ester (D46) (24.7 g) was dissolved in ethanol (450 ml) and 10% palladium on carbon (5.4 g) added. The reaction mixture was hydrogenated at atmospheric pressure for 18 h. TLC still showed starting material so additional 10% palladium on carbon (4.5 g) was added and the reaction mixture hydrogentated for a further 24 h. The mixture was filtered through a small plug of Celite (diatomaceous earth) and concentrated *in vacuo* to give the title compound (D47) as a brown oil (22.3 g, 98%). MS: m/z ($MH^+$) 352.

**Description 48**

**4-{2-[5-(2,2-Dimethoxy-ethylamino)-2-methoxy-phenoxy]-ethyl}-piperazine-1-carboxylic acid *tert*-butyl ester (D48)**

4-[2-(5-Amino-2-methoxyphenoxy)ethyl]piperazine-1-carboxylic acid *tert*-butyl ester (D47) (23.9 g) was dissolved in ethanol (370 ml) and glyoxal 1,1-dimethylacetal solution (~ 45% in *tert*-butylmethylether, 19 ml) and 10% palladium on carbon (8.0g) added. The reaction mixture was then hydrogenated at atmospheric pressure for 66 h. The mixture was filtered through a small plug of Celite (diatomaceous earth) and concentrated *in vacuo*. The residue was azeotroped with toluene to give the title compound (D48) as a brown oil (28.3 g, 95%). MS: m/z ($MH^+$) 440.

**Description 49**

**5-Methoxy-6-(2-piperazin-1-ylethoxy)-1*H*indole (D49)**

4-{2-[5-(2,2-dimethoxyethylamino)-2-methoxyphenoxy]ethyl}piperazine-1-carboxylic acid *tert*-butyl ester (D48) (10 g) was dissolved in cold trifluoroacetic acid (35 ml) and cooled to 0°C in an ice-water bath. Trifluoroacetic anhydride (35 ml) was added and the mixture stirred at ice-bath temperature for 0.75 h. The mixture was diluted with further trifluoroacetic acid (30 ml) and heated at reflux under argon for 5 h. The mixture was allowed to cool to room temperature, concentrated *in vacuo* and azeotroped with toluene. The residue was partitioned between chloroform (200 ml) and saturated sodium bicarbonate solution (250 ml). The organic layer was separated and the aqueous layer re-extracted with further chloroform (125 ml x 3). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil. The residue was dissolved in methanol (150ml) and stirred with potassium

carbonate (10.9 g) at room temperature for 6 h. The mixture was concentrated *in vacuo* and the residue partioned between chloroform (300 ml) and water (150 ml). Undissolved potassium carbonate was removed by filtration and the organic layer separated. The aqueous layer was re-extracted with chloroform (x 5) and the combined organics washed with brine solution. The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude title compound (D49) as a brown foam (6 g, 96%). MS: m/z ($MH^+$) 276.

**Description 50**

**4-[2-(Methoxy-1-*H*-indol-6-yloxy)ethyl]piperazine-1-carboxylic acid *tert*-butyl ester (D50)**

5-Methoxy-6-(2-piperazin-1-ylethoxy)-1 *H* indole (D49) (6 g) was dissolved in DCM (150 ml) and treated with triethylamine (3.6 ml) and di-*tert*-butyl carbonate (5.0 g). The reaction mixture was stirred at room temperature under argon for 3 h. The mixture was diluted with DCM (100 ml) and washed with saturated sodium bicarbonate solution (200 ml), water (200 ml) and brine (200 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo*. The brown residue was purified by column chromatography on silica gel eluting with DCM to 3% methanol/DCM to give the title compound (D50) as a yellow foam (2.6 g, 32%). MS: m/z ($MH^+$) 376.

**Description 51**

**4-[2-(5-Methoxy-2,3-dihydro-1*H*-indol-6-yloxy)ethyl]piperazine-1-carboxylic acid *tert*-butyl ester (D51)**

The title compound D51 was prepared from 4-[2-(Methoxy-1-*H*-indol-6-yloxy)ethyl]piperazine-1-carboxylic acid *tert*-butyl ester (D50) using the procedure described for the preparation of D35. MS: m/z ($MH^+$) 378.

**Description 52**

**4-(2-{1-[(*E*)-3-(2-Chlorophenyl)allanoyl]-5-methoxy-2,3-dihydro-1*H*-indol-6-yloxy}ethyl)piperazine-1-carboxylic acid *tert*-butyl ester (D52)**

The title compound D52 was prepared from 4-[2-(5-Methoxy-2,3-dihydro-1*H*-indol-6-yloxy)ethyl]piperazine-1-carboxylic acid *tert*-butyl ester (D51) using the procedure described for the preparation of D37. MS: m/z ($MH^+$) 542/544.

**Description 53**

**1-[6-(2-Piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]ethanone (D53)**

A mixture of 1-acetyl-6-hydroxyindoline[1] (1 g, 5.64 mmol), 1-(2-chloroethyl)-piperidine hydrochloride (1.14 g, 1.2 eq.) and sodium iodide (0.05 g) was heated at

reflux in a mixture of 1,2-dimethoxyethane (80 ml), saturated aqueous potassium carbonate (30 ml) and water (10 ml) for 20 h. The resulting dark brown solution was cooled and partitioned between DCM (3 x 200 ml) and dilute potassium carbonate (200 ml). The combined organics were dried ($MgSO_4$) and evaporated *in vacuo* to an oil which was purified by flash chromatography on silica gel eluting with a mixture of ammonia (1%), methanol (5%) and dichloromethane (94%) to give the title compound (D53) (0.38 g, 23% plus starting material 15%). MS m/z ($MH^+$) 289.

1. Gaster *et al*, WO 98/50346.

**Description 54**

**1-[5-Bromo-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]ethanone (D54)**

1-[6-(2-Piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]ethanone (D53) (0.38 g, 1.31 mmol) was dissolved in a mixture of DMF (6 ml) and acetic acid (6 ml). The mixture was cooled to 0°C under argon, then N-bromosuccinimide (0.28 g, 1.2 eq.) was added portionwise over 20 min. The solution was stirred for a further 30 minutes at 0°C, then neutralised with saturated aqueous potassium carbonate (25 ml). The mixture was extracted into DCM (3 x 100 ml) and the combined organics were dried ($MgSO_4$) and evaporated *in vacuo* to give the title compound (D54) as a brown oil (0.31 g, 85%). MS m/z ($MH^+$) 367/369.

**Description 55**

**5-Bromo-6-(2-piperidin-1-ylethoxy)-2,3-dihydro-1-indole (D55)**

1-[5-Bromo-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]ethanone (D54) (0.30 g, 0.82 mmol) was dissolved in 2N hydrochloric acid (50 ml) and heated at reflux for 1 h. The solution was cooled and then carefully neutralised with solid potassium carbonate and the mixture extracted with DCM (3 x 100 ml). The combined organics were dried ($MgSO_4$), and evaporated *in vacuo* to give the title compound (D55) as a brown oil (0.25 g, 92%) MS m/z ($MH^+$) 325/327.

**Description 56**

**1-(6-Hydroxy-5-iodo-2,3-dihydro-indol-1-yl)-ethanone (D56)**

1-(6-Hydroxy-2,3-dihydro-indol-1-yl)-ethanone (1g, 5.6mmol) was suspended in DMF (10mL) and glacial acetic acid (25mL). The mixture was cooled to 0°C and N-iodosuccinimide (1.4g, 6.2mmol) added portionwise. After 1 h the mixture was neutralised with saturated aqueous potassium carbonate and extracted with dichloromethane (3 x 75 mL). The combined organics were dried ($Na_2SO_4$) and

evaporated in vacuo to afford the title compound (D56) (1.05 g, 62%) MS m/z ($MH^+$) 304.

**Description 57**

**1-[5-Iodo-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-ethanone (D57)**

1-(6-Hydroxy-5-iodo-2,3-dihydro-indol-1-yl)-ethanone (D56) (5.86g, 19.3mmol) was suspended in THF (150mL) and triphenylphosphine (5.56g, 21.2 mmol), 1-piperidine-ethanol (3.07 mL, 23.2 mmol) were subsequently added followed by slow dropwise addition of a solution of diethylazodicarboxylate (3.35mL, 21.2 mmol) in THF (50 mL). Stirring was continued for 18 h. After removing the solvents in vacuo, the residue was acidified with 1M HCl (500 mL) and washed with ethyl acetate (500 mL). The aqueous layer was neutralised with saturated aqueous sodium bicarbonate and the product extracted with ethyl acetate (2 x 500 mL). The combined organics were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by silica gel chromatography eluting with 5% methanol / dichloromethane to afford the title compound (D57) as a pale yellow solid (5.74g, 72%). MS m/z ($MH^+$) 415.

**Description 58**

**1-[6-(2-Piperidin-1-yl-ethoxy)-5-vinyl-2,3-dihydro-indol-1-yl]-ethanone (D58)**

To a suspension of 1-[5-iodo-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-ethanone (D57) (1g, 2.4mmol) in dry DMF (30 mL) was added vinyltributyltin (1.06 mL, 3.6mmol), triethlamine (0.67 mL) and tetrakistriphenylphosphine palladium (0) (280mg, 0.24mmol). After degassing, the mixture was heated to 100°C for 18 h. Upon cooling, the mixture was diluted with ethyl acetate (200 mL) and extracted with 0.1M HCl (2 x 100 mL). The aqueous phase was basified with $K_2CO_3$ and extracted with dichloromethane (2 x 100 mL), dried ($MgSO_4$) and evaporated *in vacuo* to afford the title compound (D58) as a brown oil. MS m/z ($MH^+$) 315.

**Description 59**

**1-[5-Ethyl-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-ethanone (D59)**

1-[6-(2-Piperidin-1-yl-ethoxy)-5-vinyl-2,3-dihydro-indol-1-yl]-ethanone (D58) (200mg, 0.64 mmol) was dissolved in ethanol (15 mL) and hydogenated over Pd on charcoal (10%) for 24 h. The mixture was filtered through keiselguhr and evaporated in vacuo to afford the title compound (D59) (170 mg, 85%). MS m/z ($MH^+$) 317.

**Description 60**

**1-Acetyl-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-1-H-indole-5-carbonitrile (D60)**

A mixture of 1-[5-iodo-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-ethanone (D57) (0.5 g, 1.2 mmol) and copper cyanide (215 mg, 2.4 mmol) in N-methyl pyrrolidinone (5 mL) under an argon atmosphere was heated to 150°C for 16 h. The reaction mixture was poured into an aqueous ammonia solution (50 mL) and then extracted with dichloromethane (3 x 100 mL). The combined organics were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified on silica eluting with 5% methanol / dichloromethane to afford the title compound (D60) (205 mg, 55%). MS m/z ($MH^+$) 314.

**Description 61**

**1-[6-(2-Piperidin-1-yl-ethoxy)-5-trifluoromethyl-2,3-dihydro-indol-1-yl]-ethanone (D61)**

A mixture of 1-[5-iodo-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-ethanone (D57) (250mg, 0.6 mmol), potassium trifluoroacetate (165mg, 1.1 mmol) and copper (I) iodide (230mg, 1.2 mmol) in DMF (6 mL) and toluene (5 mL) were heated to 150°C with azeotropic removal of toluene for 48 hrs. After cooling to room temperature, the reaction mixture was filtered and evaporated *in vacuo*. The residue was partitioned between saturated aqueous sodium bicarbonate (20 mL) and dichloromethane (3 x 30 mL). The combined organics were dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 10% methanol / dichloromethane to afford the title compound D61 as a beige solid (100mg, 47%). MS m/z ($MH^+$) 357.

**Description 62**

**6-(2-Piperidin-1-yl-ethoxy)-2,3-dihydro-1H-indole-5-carbonitrile (D62)**

The title compound D62 was prepared from 1-acetyl-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-1-H-indole-5-carbonitrile (D60) using the procedure described for the preparation of D55. MS m/z ($MH^+$) 272.

**Description 63**

**5-Ethyl-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-1H-indole (D63)**

The title compound (D63) was prepared from 1-[5-ethyl-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-ethanone (D59) using the procedure described for preparation o f D55. MS m/z ($MH^+$) 275.

**Description 64**

**6-(2-Piperidin-1-yl-ethoxy)-5-trifluoromethyl-2,3-dihydro-1H-indole (D64a) and 6-(2-Piperidin-1-yl-ethoxy)-2,3-dihydro-1H-indole (D64b)**

The title compounds D64a and D64b were prepared from 1-[6-(2-Piperidin-1-yl-ethoxy)-5-trifluoromethyl-2,3-dihydro-indol-1-yl]-ethanone (D61) using the procedure described for the preparation of D55 with chromatographic separation on silica gel. Data for D64a MS m/z ($MH^+$) 315. Data for D64b MS m/z ($MH^+$) 247.

**Description 65**

**1-(6-Hydroxy-2,3-dihydro-pyrrolo[3,2-c]pyridin-1-yl)-ethanone (D65)**

To a solution of 2,3-dihydro-1H-pyrrolo[3,2-c]pyridin-6-ol (0.3g, 2.2mmol) in pyridine (20 mL) was added acetyl chloride (0.2g, 2.8mmol) in dichloromethane (2 mL) dropwise over 15 minutes. The resulting mixture was stirred at room temperature for 3 h. The solvent was removed *in vacuo* and ice water added to the resulting residue. The solid obtained was collected by filtration, washed with water and dried to afford the title compound D65 (0.12g, 31%). MS m/z ($MH^+$) 179.

**Description 66**

**1-(6-Chloro-2,3-dihydro-pyrrolo[3,2-c]pyridin-1-yl)-ethanone (D66)**

A solution of 1-(6-hydroxy-2,3-dihydro-pyrrolo[3,2-c]pyridin-1-yl)-ethanone (D65) (0.1g, 0.56mmol) in phosphorus oxychloride (10mL) was refluxed under argon for 5 h. Upon cooling and removal of the excess phosphorus oxychloride, the residue was dissolved in dichloromethane (50 mL), washed with saturated aqueous sodium bicarbonate and dried (MgSO4). The solvent was removed *in vacuo* to afford the title compound D66 (80mg, 58%). MS m/z ($MH^+$) 197/199.

**Description 67**

**6-(2-Piperidin-1-yl-ethoxy)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine (D67)**

A mixture of 1-(6-chloro-2,3-dihydro-pyrrolo[3,2-c]pyridin-1-yl)-ethanone (D66) (70mg, 0.36mmol) and 2-hydroxyethylpiperidine, sodium salt (1.0 mmol) in DMF (20 mL) was heated to 190°C for 19 h. Upon cooling, the solvent was removed *in vacuo* and the residue co-evaporated with toluene (1 x 10 mL). The resulting solid was stirred with ethyl acetate for 20 min and filtered, washing the solid with further ethyl acetate. The combined organics were evaporated to give the title compound D67 (30mg, 34%). MS m/z (M+Na) 270.

**Description 68**

**5-(2,2-Dimethoxy-ethylamino)-2-fluoro-phenol (D68)**

To a solution of 5-amino-2-fluoro-phenol (3.0g, 23.6 mmol) and glyoxal-1,1-dimethyl acetal (45% aqueous solution) (5.2g, 52mmol) in glacial acetic acid (10 mL) and methanol (120 mL) was added sodium borohydride (3.0 g, 47.2 mmol) portionwise

over 1 h. After an additional 1 h toluene was added and the reaction mixture evaporated to a small volume. Water (60 mL) was added and the product was extracted into ethyl acetate (5 x 40 mL). The solvent was evaporated *in vacuo* and the residue co-evaporated with toluene to afford the title compound D68 (5.1 g, 95%). MS m/z (M-OMe) 184.

**Description 69**

**(2,2-Dimethoxy-ethyl)-[4-fluoro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-amine (D69)**

To a solution of 5-(2,2-dimethoxy-ethylamino)-2-fluoro-phenol (D68) (0.17g, 0.8 mmol), triphenylphosphine (0.21g, 0.8 mmol) and 1-(2-hydroxyethyl)piperidine (0.104g, 0.8 mmol) in THF under argon was added diethylazodicarboxylate (0.16g, 0.9 mmol). The resulting mixture was stirred at room temperature for 36 h. After removal of the solvent *in vacuo*, the residue was purified by chromatography on silica gel to afford the title compound (D69) (0.145g, 69%). MS m/z ($MH^+$) 327.

**Description 70**

**N-(2,2-Dimethoxy-ethyl)-2,2,2-trifluoro-N-[4-fluoro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-acetamide (D70)**

A solution of (2,2-dimethoxy-ethyl)-[4-fluoro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-amine (D69) in dichloromethane (10 mL) and hexane (10 mL) at 0°C was treated with triethylamine (0.05g, 0.5mmol) and trifluoroaceticanhydride (105mg, 0.5mmol). Stirring was continued for 1 h at 0°C before allowing to warm to room temperature over 1 h. The reaction mixture was diluted with dichloromethane (50mL) and then washed with saturated aqueous sodium bicarbonate (50 mL). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to afford the title compound D70 (0.13g, 91%). MS m/z ($MH^+$) 423.

**Description 71**

**2,2,2-Trifluoro-1-[5-fluoro-6-(2-piperidin-1-yl-ethoxy)-indol-1-yl]-ethanone (D71)**

A solution of N-(2,2-dimethoxy-ethyl)-2,2,2-trifluoro-N-[4-fluoro-3-(2-piperidin-1-yl-ethoxy)-phenyl]-acetamide (D70) (0.12g) in trifluoroacetic anhydride (8 mL) and trifluoroacetic acid (16 mL) under argon was heated to 55°C for 84 h. The solvents were removed *in vacuo* and the resulting residue co-evaporated with toluene (2 x 1mL) to afford the title compound D71 (0.11g). MS m/z ($MH^+$) 359.

**Description 72**

**5-Fluoro-6-(2-piperidin-1-yl-ethoxy)-1H-indole (D72)**

A solution of 2,2,2-trifluoro-1-[5-fluoro-6-(2-piperidin-1-yl-ethoxy)-indol-1-yl]-ethanone (D71) (110mg) and potassium carbonate (0.2g) in methanol was stirred at room temperature for 2 h. After removal of the solvent, the residue was treated with water (20 mL) and the product was extracted with ethyl acetate (3 x 10 mL). The combned organics were dried (MgSO4) and evaporated *in vacuo* to afford the title compound D72 (100mg). MS m/z ($MH^+$) 263.

**Description 73**

**5-Fluoro-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-1H-indole (D73)**

The title compound was prepared from 5-fluoro-6-(2-piperidin-1-yl-ethoxy)-1H-indole (D72) ) according to the procedure described for preparation of D13.

**Example 1**

**(E)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]propenone (E1)**

A solution of 5-methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydro-1*H*-indole (D13) (100 mg), 2-chlorocinnamic acid (87 mg), 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (180 mg), diisopropylamine (0.32 ml) in DMF (1 ml) was stirred at room temperature for 12 h. The solution was then concentrated *in vacuo* and the residue dissolved in DCM (50 ml) and then washed with saturated aqueous potassium carbonate solution (20 ml) and water (20 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a residue which was purified by column chromatography on silica gel, eluting with 10% methanol in DCM to give the title compound (E1) as a gum (90 mg, 40%). $^1H$ (400 MHz, $CD_3OD$), $\delta_H$ 1.73 (2H, s), 1.92 (4H, s), 3.23 (6H, m), 3.54 (2H, s), 3.88 (3H, s), 4.41 (4H, m), 7.03 (1H, s), 7.16 (1H, d, *J* 16.0), 7.57 (2H, m), 7.95 (1H, m), 8.27 (2H, m), 8.61 (1H, d, *J* 16.0). MS m/z ($MH^+$) 441 / 443.

**Example 2**

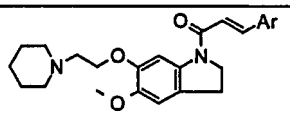
**(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]propenone hydrochloride (E2)**

(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]propenone (E1) (90 mg) was dissolved in DCM (15 ml) and treated with 1M ethereal hydrochloric acid (~0.2 ml) until just acidic. The solution was cooled in ice for 10 min. and the precipitate was filtered-off to give the title compound (E2) as a yellow solid (77 mg, 86%). $^1H$ (250 MHz, DMSO-$d_6$), δ 1.73 (2H, m), 1.81 (4H, m), 3.01 (4H, m), 3.15 (2H, t, *J* 8.3), 3.44 (2H, m), 3.77 (3H, s), 4.34 (4H, m), 7.01 (1H,

s), 7.17 (1H, d, *J* 15.0), 7.43 (2H, m), 7.57 (1H, m), 7.98 (1H, d, *J* 15.0), 8.06 (2H, m), 9.97 (1H, s). MS m/z ($MH^+$) 441 / 443.

Examples E3 - E33 in Table 1 were prepared from 5-methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydro-1*H*-indole (D13) and the appropriately substituted cinnamic acid in a similar manner to that for E1.

**Table 1**

|  | **NMR $^1H$ (400 MHz, $CD_3OD$) δ:** | **MS ($MH^+$)** |
|---|---|---|
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-napthalen-1-yl-propenone (E3) | 1.73 (2H, s), 1.92 (4H, s), 3.23 (6H, m), 3.54 (2H, s), 3.88 (3H, s), 4.41 (4H, m), 7.03 (1H, s), 7.16 (1H, d, *J* 16.0), 7.57 (3H, m), 7.95 (3H, m), 8.27 (2H, m), 8.61 (1H, d, *J* 16.0). | 457 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2,3,5-trifluorophenyl)propenone (E4) | 1.50 (2H, s), 1.71(4H, s), 2.75 (4H, s), 3.03 (2H, m), 3.20 (2H, s), 3.83 (3H, s), 4.27 (4H, m), 6.94 (4H, m), 7.80 (1H, d, *J* 16.0), 8.11 (1H, s) | 461 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2,3,6-trichlorophenyl)propenone (E5) | 1.50 (2H, s), 1.71(4H, s), 2.75 (4H, s), 3.03 (2H, m), 3.20 (2H, s), 3.83 (3H, s), 4.27 (4H, m), 6.94 (2H, m), (2H, d, *J* 16.0), 7.80 (1H, d, *J* 16.0), 8.11 (1H, s) | 509/511/ 513/515 |
| *E*-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydro-indol-1-yl]-2-methylpropenone hydrochloride (E6) | 1.44 (2H, s), 1.59 (4H, s), 2.06 (3H, s), 2.53 (4H, m), 2.84 (2H, s), 3.10 (2H, t, *J* 8.0), 3.83 (3H, s), 4.22 (4H, m), 6.78 (2H, s), 7.27 (3H, m), 7.41 (2H, m) | 455/457 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1- | 1.44 (2H, s), 1.59 (4H, s), | 505 |

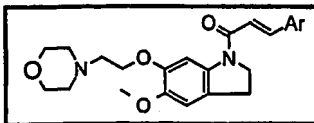
| | | |
|---|---|---|
| ylethoxy)-2,3-dihydroindol-1-yl]-2-methyl-3-(2-trifluoromethoxyphenyl)-propenone hydrochloride (E7) | 2.06 (3H, s), 2.53 (4H, s), 2.84 (2H, s), 3.10 (2H, t, *J* 8.0), 3.83 (3H, s, OMe), 4.22 (4H, m, $OCH_2$, ind-$CH_2$), 6.78 (2H, s, Ar-*H*), 7.27 (3H, m, Ar-*H*), 7.41 (2H, m, cin-H, Ar-*H*). | |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2-trifluoromethoxyphenyl)-propenone (E8) | 1.44 (2H, s), 1.59 (4H, s), 2.53 (4H, s), 2.84 (2H, s), 3.10 (2H, t, *J* 8.0), 3.83 (3H, s), 4.22 (4H, m), 6.78 (2H, s), 6.95 (1H, d, *J* 16.0), 7.27 (3H, m), 7.41 (2H, m), 8.14 (1H, d, *J* 16.0) | 491 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-phenyl-propenone (E9) | 1.46 (2H, s), 1.62 (4H, s), 2.56 (4H, s), 2.86 (2H, t, *J* 6.0), 3.17 (2H, t, *J* 8.4), 3.83 (3H, s), 4.24 (4H, m), 6.74 (1H, s), 6.84 (1H, d, *J* 15.2), 7.39 (3H, m), 7.58 (2H, m), 7.82 (1H, d, *J* 15.2), 8.14 (1H, s) | 407 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2-bromophenyl)-propenone (E10) | | 485/487 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2-bromo-5-fluorophenyl)-propenone (E11) | | 503/505 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2,4-dichlorophenyl)-propenone (E12) | | 475/477/479 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2,3-dichlorophenyl)-propenone (E13) | | 475/477/479 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2,6-dichlorophenyl)-propenone (E14) | | 475/477/479 |

| | | |
|---|---|---|
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2-chloro-4-fluorophenyl)-propenone (E15) | | 459/461 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2-chloro-6-fluorophenyl)-propenone (E16) | | 459/461 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2,6-difluorophenyl)-propenone (E17) | | 443 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2-trifluoromethylphenyl)-propenone (E18) | | 475 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2-cyanophenyl)-propenone (E19) | | 432 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2-phenethylthiophenyl)-propenone (E20) | | 543 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2-methanesulphonylphenyl)-propenone (E21) | | 485 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl-3-(2,3,6-trichloro-phenyl)-propenone (E22) | | 523/525/527/529 |
| *E*-3-(2,3-Dichloro-phenyl)-1-[5-methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl propenone (E23) | | 489/491/493 |
| *E*-3-(2,6-Difluoro-phenyl)-1-[5-methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl propenone (E24) | | 457 |
| *E*-3-(2,4-Dichloro-phenyl)-1-[5-methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl propenone (E25) | | 489/491/493 |

| | | |
|---|---|---|
| *E*-3-(4-Chloro-phenyl)-1-[5-methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl-propenone (E26) | | 455/457 |
| *E*-3-(4-Fluoro-phenyl)-1-[5-methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl-propenone (E27) | | 439 |
| *E*-3-(2-Chloro-3,6-difluoro-phenyl)-1-[5-methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl-propenone (E28) | | 491/493 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl-3-(2,3,5-trifluoro-phenyl)-propenone (E29) | | 475 |
| *E*-3-(2-Bromo-phenyl)-1-[5-methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl-propenone (E30) | | 499/501 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl-3-phenyl-propenone (E31) | | 421 |
| *E*-1-[5-Methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-phenyl-but-2-en-1-one (E32) | | 421 |
| *E*-3-(2,6-Dichloro-phenyl)-1-[5-methoxy-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-2-methyl-propenone (E33) | | 489/491/493 |

Examples E34 to E57 in **Table 2** were prepared from 5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-1H-indole (D15) and the appropriately substituted cinnamic acid in a similar manner to that for E1.

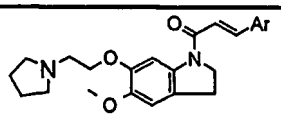
**Table 2**

|  | MS (MH⁺) |
|---|---|
| (E)-3-(2-Chloro-6-fluoro-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E34) | 461/463 |
| (E)-3-(2-Bromo-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E35) | 487/489 |
| (E)-3-(2,6-Dichloro-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E36) | 477/479/ 481 |
| (E)-1-[5-Methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2,3,6-trichloro-phenyl)-propenone (E37) | 511/513/ 515/517 |
| (E)-3-(2,4-Dichloro-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E38) | 477/479/ 481 |
| (E)-3-(2,6-Difluoro-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E39) | 445 |
| (E)-(5-Fluoro-2-trifluoromethyl-phenyl)-[methoxy-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E40) | 495 |
| (E)-3-(2-Chloro-4-fluoro-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E41) | 461/463 |
| (E)-1-[5-Methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2,3,5-trifluoro-phenyl)-propenone (E42) | 463 |
| (E)-1-[5-Methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2,3,6-trifluoro-phenyl)-propenone (E43) | 463 |
| (E)-3-(5-Bromo-2-methoxy-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E44) | 517/519 |
| (E)-3-(5-Bromo-2-ethoxy-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E45) | 531/533 |
| (E)-1-[5-Methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-phenyl-propenone (E46) | 409 |
| (E)-1-[5-Methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2-phenoxy-phenyl)-propenone (E47) | 501 |
| (E)-3-(3-Chloro-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E48) | 443/445 |
| (E)-3-(6-Bromo-benzo[1,3]dioxol-5-yl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E49) | 531/533 |
| (E)-3-(3,5-Difluoro-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E50) | 445 |

| | |
|---|---|
| (E)-1-[5-Methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-naphthalen-1-yl-propenone (E51) | 459 |
| (E)-3-(5-Bromo-2-fluoro-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E52) | 505/507 |
| (E)-3-(4-Chloro-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E53) | 443/445 |
| (E)-1-[5-Methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2,4,5-trifluoro-phenyl)-propenone (E54) | 463 |
| (E)-3-(2-Ethoxy-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E55) | 453 |
| (E)-1-[5-Methoxy-6-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2-trifluoromethoxy-phenyl)-propenone (E56) | 493 |
| (E)-1-[Methoxy-(2-morpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2-trifluoromethyl-phenyl)-propenone (E57) | 477 |

Examples E58 to E78 in **Table 3** were prepared from 5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-1H-indole (D14) and the appropriately substituted cinnamic acid in a similar manner to that for E1.

**Table 3**

|  | MS ($MH^+$) |
|---|---|
| (E)-3-(2-Bromo-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E58) | 471/473 |
| (E)-3-(2-Chloro-6-fluoro-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E59) | 445/447 |
| (E)-3-(2,4-Dichloro-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E60) | 461/463/465 |
| (E)-3-(2,6-Difluoro-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E61) | 429 |
| (E)-3-(2,6-Dichloro-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E62) | 461/463/465 |
| (E)-3-(2-Chloro-4-fluoro-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E63) | 445/447 |

| | |
|---|---|
| (E)-1-[5-Methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2,3,6-trichloro-phenyl)-propenone (E64) | 495/497/ 499/501 |
| (E)-3-(5-Bromo-2-ethoxy-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E65) | 515/517 |
| (E)-1-[5-Methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2,3,5-trifluoro-phenyl)-propenone (E66) | 447 |
| (E)-3-(6-Bromo-benzo[1,3]dioxol-5-yl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E67) | 515/517 |
| (E)-3-(5-Bromo-2-methoxy-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E68) | 501/503 |
| (E)-1-[5-Methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-phenyl-propenone (E69) | 393 |
| (E)-3-(3-Chloro-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E70) | 427/429 |
| (E)-1-[5-Methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2-phenoxy-phenyl)-propenone (E71) | 485 |
| (E)-1-[5-Methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-naphthalen-1-yl-propenone (E72) | 443 |
| (E)-3-(3,5-Difluoro-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E73) | 429 |
| (E)-3-(5-Bromo-2-fluoro-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E74) | 489/491 |
| (E)-3-(4-Chloro-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E75) | 427/429 |
| (E)-3-(2-Ethoxy-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E76) | 437 |
| (E)-3-(2-Bromo-4,5-dimethoxy-phenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E77) | 531/533 |
| (E)-1-[5-Methoxy-6-(2-pyrrolidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-3-(2,4,5-trifluoro-phenyl)-propenone (E78) | 447 |

**Example 79**

**(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-morpholin-4-ylethoxy)-2,3-dihydro-indol-1-yl]propenone (E79)**

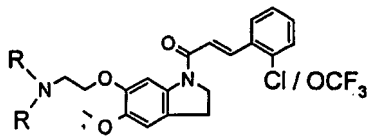
A mixture of methanesulfonic acid 2-{1-[(*E*)-3-(2-chlorophenyl)allanoyl]-5-methoxy-2,3-dihydro-1*H*-indol-6-yloxy}ethyl ester (D38) (63 mg, 0.14 mmol), 4-

piperidinopiperidine (42 mg, 0.25 mmol), sodium iodide (38 mg, 0.25 mmol) and anhydrous potassium carbonate (140 mg, 1 mmol) in DMF (10 ml), was heated at 60°C for 17 h. The solvent was removed, the residue was partitioned between DCM (30 ml) and water (10 ml). The organic phase was dried ($MgSO_4$), the solvent was evaporated and the product was purified by column chromatography on silica gel (eluting with DCM–methanol gradient) to give the title compound (E79) as a yellow solid (57 mg, 78%).

$^1H$ (250 MHz, $CDCl_3$) δ1.43 (5H, br. m),1.90 (4 H, m), 2.27 (6 H, m), 2.85 (2 H, m), 3.21 (6 H, m), 3.85 (3 H, s), 4.16 (2 H, m), 4.30 (2 H, t, *J* 8.4 Hz), 6.77 (1 H, s,), 6.86 (1 H, d, *J* 15.5 Hz), 7.30 (2 H, m), 7.36 (1 H, m), 7.42 (1 H, m), 8.16 (1 H, d, *J* 15.5 Hz), 8.18 (1 H, s); MS: m/z ($MH^+$) = 524/526.

Examples E80 to E156 in **Table 4** were prepared from methanesulfonic acid 2-{1-[(*E*)-3-(2-chlorophenyl)allanoyl]-5-methoxy-2,3-dihydro-1*H*-indol-6-yloxy}ethyl ester (D38) or methanesulfonic acid 2-{5-methoxy-1-[(*E*)-3-(2-trifluoromethoxy-phenyl)allanoyl]-2,3-dihydro-1*H*-indol-6-yloxy}-ethyl ester (D42) and the appropriate amines as described above for E79.

**Table 4**

|  | **MS ($MH^+$)** |
|---|---|
| (*E*)-1-[6-(2-[1,4']Bipiperidinyl-1'-ylethoxy)-5-methoxy-2,3-dihydroindol-1-yl]-3-(2-chlorophenyl)propenone (E80) | 524/526 |
| (*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-ylethoxy)-2,3-dihydroindol-1-yl]propenone (E81) | 427/429 |
| (*E*)-3-(2-Chlorophenyl)-1-{6-[2-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)ethoxy]-5-methoxy-2,3-dihydroindol-1-yl}propenone (E82) | 499/501 |
| (*E*)-3-(2-Chlorophenyl)-1-{6-[2-(3,5-dimethylpiperidin-1-yl)ethoxy]-5-methoxy-2,3-dihydroindol-1-yl}propenone (E83) | 469/471 |
| (*E*)-3-(2-Chlorophenyl)-1-{6-[2-(2,6-dimethylpiperidin-1-yl)-ethoxy]-5-methoxy-2,3-dihydroindol-1-yl}propenone (E84) | 469/471 |
| (*E*)-3-(2-Chlorophenyl)-1-{5-methoxy-6-[2-(3-methylamino-pyrrolidin-1-yl)ethoxy]-2,3-dihydroindol-1-yl}propenone hydrochloride salt (E85) | 456/458 |
| 1-(2-{1-[(*E*)-3-(2-Chlorophenyl)allanoyl]-5-methoxy-2,3-dihydro-1*H*- | 513/515 |

| | |
|---|---|
| indol-6-yloxy}ethyl)piperidine-4-carboxylic acid ethyl ester (E86) | |
| 1-(2-{1-[(*E*)-3-(2-Chlorophenyl)allanoyl]-5-methoxy-2,3-dihydro-1*H*-indol-6-yloxy}ethyl)piperidine-4-carboxylic acid amide (E87) | 484/486 |
| (*E*)-3-(2-Chlorophenyl)-1-{6-[2-(4-hydroxy-4-phenylpiperidin-1-yl)-ethoxy]-5-methoxy-2,3-dihydroindol-1-yl}propenone (E88) | 533/535 |
| (*E*)-3-(2-Chlorophenyl)-1-{6-[2-(4-hydroxymethyl-piperidin-1-yl)-ethoxy]-5-methoxy-2,3-dihydroindol-1-yl}propenone (E89) | 471/473 |
| (*E*)-1-{6-[2-(4-Benzylpiperidin-1-yl)ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-3-(2-chlorophenyl)propenone (E90) | 531/533 |
| (*E*)-3-(2-Chlorophenyl)-1-{5-methoxy-6-[2-(4-pyrrolidin-1-yl-piperidin-1-yl)ethoxy]-2,3-dihydro-indol-1-yl}propenone (E91) | 510/512 |
| (*E*)-3-(2-Chlorophenyl)-1-{6-[2-((R)-3-hydroxypyrrolidin-1-yl)-ethoxy]-5-methoxy-2,3-dihydroindol-1-yl}propenone (E92) | 443/445 |
| (*E*)-3-(2-Chlorophenyl)-1-{5-methoxy-6-[2-((S)-2-methoxymethyl-pyrrolidin-1-yl)ethoxy]-2,3-dihydro-indol-1-yl}propenone (E93) | 471/473 |
| (*E*)-3-(2-Chlorophenyl)-1-{6-[2-((R)-3-dimethylaminopyrrolidin-1-yl)ethoxy]-5-methoxy-2,3-dihydroindol-1-yl}propenone (E94) | 470/472 |
| (*E*)-3-(2-Chlorophenyl)-1-{5-methoxy-6-[2-(4-methylpiperidin-1-yl)-ethoxy]-2,3-dihydroindol-1-yl}propenone (E95) | 455/457 |
| (*E*)-3-(2-Chlorophenyl)-1-(5-methoxy-6-{2-[4-(2-methoxyphenyl)-piperidin-1-yl]ethoxy}-2,3-dihydroindol-1-yl)propenone (E96) | 547/549 |
| (*E*)-1-{6-[2-(4-Aminopiperidin-1-yl)ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-3-(2-chlorophenyl)propenone hydrochloride salt (E97) | 456/458 |
| (*E*)-3-(2-Chlorophenyl)-1-{6-[2-(1,5-dioxa-9-azaspiro[5.5]undec-9-yl)ethoxy]-5-methoxy-2,3-dihydroindol-1-yl}propenone (E98) | 513/515 |
| (*E*)-1-{6-[2-(3,5-Dimethylpiperidin-1-yl)ethoxy]-5-methoxy-2,3-dihydroindol-1-yl}-3-(2-trifluoromethoxyphenyl)propenone (E99) | 519 |
| (*E*)-1-[6-(2-[1,4']Bipiperidinyl-1'-yl-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-3-(2-trifluoromethoxyphenyl)propenone (E100) | 574 |
| (*E*)-1-{6-[2-(1,5-Dioxa-9-azaspiro[5.5]undec-9-yl)ethoxy]-5-methoxy-2,3-dihydroindol-1-yl}-3-(2-trifluoromethoxy-phenyl)propenone (E101) | 563 |
| (*E*)-1-{5-Methoxy-6-[2-(4-methylpiperidin-1-yl)ethoxy]-2,3-dihydro-indol-1-yl}-3-(2-trifluoromethoxyphenyl)propenone (E102) | 505 |
| (*E*)-1-(5-Methoxy-6-{2-[4-(2-methoxyphenyl)piperidin-1-yl]ethoxy}-2,3-dihydroindol-1-yl)-3-(2-trifluoromethoxyphenyl)propenone | 597 |

| | |
|---|---|
| (E103) | |
| (*E*)-1-{5-Methoxy-6-[2-((S)-2-methoxymethylpyrrolidin-1-yl)-ethoxy]-2,3-dihydroindol-1-yl}-3-(2-trifluoromethoxyphenyl)-propenone (E104) | 521 |
| (E)-3-(2-Chloro-phenyl)-1-{5-methoxy-6-[2-(2-methyl-piperidin-1-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone (E105) | 455/457 |
| (E)-3-(2-Chloro-phenyl)-1-{6-[2-(4,4-difluoro-piperidin-1-yl)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-propenone (E106) | 477/479 |
| (E)-3-(2-Chloro-phenyl)-1-{5-methoxy-6-[2-(4-methoxymethyl-piperidin-1-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone (E107) | 485/487 |
| (*E*)-3-(2-Chlorophenyl)-1-{5-methoxy-6-[2-(4-methylpiperazin-1-yl)-ethoxy]-2,3-dihydroindol-1-yl}propenone (E108) | 456/458 |
| 2-[4-(2-{1-[(*E*)-3-(2-Chlorophenyl)allanoyl]-5-methoxy-2,3-dihydro-1*H*-indol-6-yloxy}ethyl)piperazin-1-yl]-1-pyrrolidin-1-ylethanone (E109) | 553/555 |
| (*E*)-3-(2-Chlorophenyl)-1-(5-methoxy-6-{2-[4-(2-morpholin-4-yl-ethyl)piperazin-1-yl]ethoxy}-2,3-dihydroindol-1-yl)propenone (E110) | 555/557 |
| [4-(2-{1-[(*E*)-3-(2-Chlorophenyl)allanoyl]-5-methoxy-2,3-dihydro-1*H*-indol-6-yloxy}ethyl)piperazin-1-yl]-acetic acid ethyl ester (E111) | 528/530 |
| (*E*)-3-(2-Chlorophenyl)-1-(6-{2-[4-(2-hydroxyethyl)-piperazin-1-yl]-ethoxy}-5-methoxy-2,3-dihydroindol-1-yl)propenone (E112) | 486/488 |
| (*E*)-3-(2-Chlorophenyl)-1-(5-methoxy-6-{2-[4-(2-pyrrolidin-1-yl-ethyl)piperazin-1-yl]ethoxy}-2,3-dihydroindol-1-yl)propenone (E113) | 539/541 |
| (*E*)-3-(2-Chlorophenyl)-1-(5-methoxy-6-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]ethoxy}-2,3-dihydroindol-1-yl)propenone (E114) | 539/541 |
| (E)-3-(2-Chloro-phenyl)-1-{5-methoxy-6-[2-(4-pyridin-2-ylmethyl-piperazin-1-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone (E115) | 533/535 |
| (E)-3-(2-Chloro-phenyl)-1-(6-{2-[4-(3-fluoro-propyl)-piperazin-1-yl]-ethoxy}-5-methoxy-2,3-dihydro-indolin-1-yl)-propenone (E116) | 502/504 |
| 2-[4-(2-{1-[(E)-3-(2-Chloro-phenyl)-allanoyl]-5-methoxy-2,3-dihydro-1 *H*-indol-6-yloxy}-ethyl)-piperazin-1-yl]-N,N-dimethyl-acetamide (E117) | 527/529 |
| 4-(2-{1-[(E)-3-(2-Chloro-phenyl)-allanoyl]-5-methoxy-2,3-dihydro-1 H-indol-6-yloxy}-ethyl)-piperazine-1-carboxylic acid tert butyl ester (E118) | 542/544 |
| (E)-3-(2-Chloro-phenyl)-1-[6-(2-{4-[2-(1 H-indol-3-yl)-ethyl]- | 585/587 |

| | |
|---|---|
| piperazin-1-yl}-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-propenone (E119) | |
| (E)-3-(2-Chloro-phenyl)-1-(5-methoxy-6-{2-[4-(3,3,3-trifluoro-propyl)-piperazin-1-yl]-ethoxy}-2,3-dihydro-indol-1-yl)-propenone (E120) | 538/540 |
| (E)-1-(6-{2-[4-(1H-Benzoimidazol-2-ylmethyl)-piperazin-1-yl]-ethoxy}-5-methoxy-2,3-dihydro-indol-1-yl)-3-(2-chloro-phenyl)-propenone (E121) | 572/574 |
| 3-[4-(2-{1-[(E)-3-(2-Chloro-phenyl)-allanoyl]-5-methoxy-2,3-dihydro-1H-indol-6-yloxy}-ethyl)-piperazin-1-yl]-propionitrile (E122) | 495/497 |
| (E)-3-(2-Chloro-phenyl)-1-(5-methoxy-6-{2-[4-(3-methyl-butyl)-piperazin-1-yl]-ethoxy}-2,3-dihydro-indol-1-yl)-propenone (E123) | 512/514 |
| (E)-3-(2-Chloro-phenyl)-1-(5-methoxy-6-{2-[4-(2-oxo-propyl)-piperazin-1-yl]-ethoxy}-2,3-dihydro-indol-1-yl)-propenone (E124) | 512/514 |
| (E)-3-(2-Chloro-phenyl)-1-(5-methoxy-6-{2-[4-(2-phenoxy-ethyl)-piperazin-1-yl]-ethoxy}-2,3-dihydro-indol-1-yl)-propenone (E125) | 562/564 |
| (E)-3-(2-Chloro-phenyl)-1-{5-methoxy-6-[2-(4-phenethyl-piperazin-1-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone (E126) | 546/548 |
| (E)-3-(2-Chloro-phenyl)-1-{5-methoxy-6-[2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone (E127) | 455/457 |
| (E)-3-(2-Chloro-phenyl)-1-{5-methoxy-6-[2-(2-methyl-morpholin-4-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone (E128) | 457/459 |
| (E)-3-(2-Chloro-phenyl)-1-(6-{2-[3-(2-hydroxy-ethyl)-morpholin-4-yl]-ethoxy}-5-methoxy-2,3-dihydro-indol-1-yl)-propenone (E129) | 487/489 |
| (E)-3-(2-Chloro-phenyl)-1-{6-[2-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-propenone (E130) | 471/473 |
| (E)-3-(2-Chloro-phenyl)-1-{5-methoxy-6-[2-(2-phenyl-morpholin-4-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone (E131) | 519/521 |
| (E)-3-(2-Chloro-phenyl)-1-{5-methoxy-6-[2-(2-phenoxymethyl-morpholin-4-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone (E132) | 549/551 |
| (E)-3-(2-Chloro-phenyl)-1-(5-methoxy-6-{2-[2-(4-methoxy-benzyloxy)-morpholin-4-yl]-ethoxy}-2,3-dihydro-indol-1-yl)-propenone (E133) | 579/581 |
| (E)-3-(2-Chloro-phenyl)-1-[5-methoxy-6-(2-thiomorpholin-4-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E134) | 459/461 |

| | |
|---|---|
| (E)-3-(2-Chloro-phenyl)-1-{6-[2-(2-hydroxymethyl-piperidin-1-yl)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-propenone (E135) | 471/473 |
| (E)-3-(2-Chloro-phenyl)-1-[6-(2-diisopropylamino-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-propenone (E136) | 457/459 |
| (E)-1-[6-(2-Azepan-1-yl-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-3-(2-chloro-phenyl)-propenone (E137) | 455/457 |
| (E)-1-{6-[2-(tert-Butyl-methyl-amino)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-3-(2-chloro-phenyl)-propenone (E138) | 443/445 |
| (E)-3-(2-Chloro-phenyl)-1-{6-[2-(isopropyl-methyl-amino)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-propenone (E139) | 429/431 |
| (E)-3-(2-Chloro-phenyl)-1-{6-[2-(ethyl-isopropyl-amino)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-propenone (E140) | 443/445 |
| (E)-3-(2-Chloro-phenyl)-1-{6-[2-(ethyl-methyl-amino)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-propenone (E141) | 415/417 |
| (E)-1-{6-[2-(Butyl-methyl-amino)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-3-(2-chloro-phenyl)-propenone (E142) | 443/445 |
| (E)-3-(2-Chloro-phenyl)-1-[6-(2-diethylamino-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-propenone (E143) | 429/431 |
| (E)-3-(2-Chloro-phenyl)-1-[6-(2-dimethylamino-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-propenone (E144) | 401/403 |
| (E)-1-{6-[2-(8-Aza-bicyclo[3.2.1]oct-8-yl)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-3-(2-chloro-phenyl)-propenone (E145) | 481/483 |
| (E)-3-(2-Chloro-phenyl)-1-(5-methoxy-6-{2-[(2-methoxy-ethyl)-methyl-amino]-ethoxy}-2,3-dihydro-indol-1-yl)-propenone (E146) | 445/447 |
| (E)-1-(6-{2-[Bis-(2-methoxy-ethyl)-amino]-ethoxy}-5-methoxy-2,3-dihydro-indol-1-yl)-3-(2-chloro-phenyl)-propenone (E147) | 489/491 |
| 3-[(2-{1-[(E)-3-(2-Chloro-phenyl)-allanoyl]-5-methoxy-2,3-dihydro-1H-indol-6-yloxy}-ethyl)-methyl-amino]-propionitrile (E148) | 440/442 |
| 3-[(2-{1-[(E)-3-(2-Chloro-phenyl)-allanoyl]-5-methoxy-2,3-dihydro-1H-indol-6-yloxy}-ethyl)-ethyl-amino]-propionitrile (E149) | 454/456 |
| (E)-3-(2-Chloro-phenyl)-1-{6-[2-([1,3]dioxolan-2-ylmethyl-methyl-amino)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-propenone (E150) | 473/475 |
| (E)-3-(2-Chloro-phenyl)-1-(6-{2-[(2-hydroxy-1,1-dimethyl-ethyl)-methyl-amino]-ethoxy}-5-methoxy-2,3-dihydro-indol-1-yl)-propenone (E151) | 459/461 |
| (E)-3-(2-Chloro-phenyl)-1-[6-(2-dibutylamino-ethoxy)-5-methoxy- | 485/487 |

| | |
|---|---|
| 2,3-dihydro-indol-1-yl]-propenone (E152) | |
| (E)-3-(2-Chloro-phenyl)-1-{6-[2-(di-sec-butyl-amino)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-propenone (E153) | 485/487 |
| (E)-3-(2-Chloro-phenyl)-1-(6-{2-[isopropyl-(2-methoxy-ethyl)-amino]-ethoxy}-5-methoxy-2,3-dihydro-indol-1-yl)-propenone (E154) | 473/475 |
| (E)-3-(2-Chloro-phenyl)-1-(6-{2-[ethyl-(2-methoxy-ethyl)-amino]-ethoxy}-5-methoxy-2,3-dihydro-indol-1-yl)-propenone (E155) | 459/461 |
| (*E*)-1-[5-Methoxy-6-(2-pyrrolidin-1-ylethoxy)-2,3-dihydroindol-1yl]-3-(2-trifluoromethoxyphenyl)propenone (E156). $^1$H (250 MHz, $CDCl_3$) δ 1.82 (4 H, m), 2.68 (4 H, m), 2.99 (2 H, t, *J* 5.98 Hz), 3.20 (2 H, t, *J* 8.33 Hz), 3.84 (3 H, s), 4.24 (4 H, m), 6.75 (1 H, s), 6.94 (1 H, d, *J* 15.5 Hz), 7.36 (3 H, m), 7.65 (1 H, m), 7.97, (1 H, d, *J* 15.5 Hz), 8.14 (1 H, s); MS: m/z ($MH^+$) = 477/478. | 477 |

**Example 157**

**(E)-3-(2,4-Dichloro-phenyl)-1-{5-methoxy-6-[2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone (E157)**

The title compound (E157) was prepared from methanesulfonic acid 2-{1-[(E)-3-(2,4-dichloro-phenyl)-allanoyl]-5-methoxy-2,3-dihydro-1H-indol-6-yloxy}-ethyl ester (D40) and 2-oxa-5-aza-bicyclo[2.2.1]heptane using the procedure described for the preparation of E79. MS: m/z ($MH^+$) 441/443.

**Example 158**

**(E)-3-(2,4-Dichloro-phenyl)-1-[6-(2-dimethylamino-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-propenone (E158)**

The title compound (E158) was prepared from methanesulfonic acid 2-{1-[(E)-3-(2,4-dichloro-phenyl)-allanoyl]-5-methoxy-2,3-dihydro-1H-indol-6-yloxy}-ethyl ester (D40) and dimethylamine using the procedure described for the preparation of E79. MS: m/z ($MH^+$) 435/437/439.

**Example 159**

**(E)-3-(2-Chloro-phenyl)-1-[5-methoxy-6-(2-morpholin-4-yl-ethoxy)-indol-1-yl]-propenone (E159)**

The title compound was prepared from 5-methoxy-6-(2-morpholin-4-yl-ethoxy)-1H-indole (D12) and 2-chlorocinnamoyl chloride according to the procedure described for the preparation of D37. MS: m/z ($MH^+$) 441/443.

**Example 160**

**(E)-3-(2-Chloro-phenyl)-1-[5-methoxy-6-(2-piperidin-1-yl-ethoxy)-indol-1-yl]-propenone (E160)**

The title compound was prepared from 5-methoxy-6-(2-piperidin-1-ylethoxy)-1*H*-indole (D10) and 2-chloro cinnamoyl chloride according to the procedure described for the preparation of D37. MS: m/z ($MH^+$) 439/441.

**Example 161**

**(E)-3-(2-Chloro-phenyl)-1-[5-ethyl-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E161)**

The title compound was prepared from 5-ethyl-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-1H-indole (D63) and 2-chlorocinnamoyl chloride according to the procedure described for the preparation of D37. MS: m/z ($MH^+$) 439/441.

**Example 162**

**1-[(E)-3-(2-Chloro-phenyl)-allanoyl]-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-1H-indole-5-carbonitrile (E162)**

The title compound was prepared from 6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-1H-indole-5-carbonitrile (D62) and 2-chlorocinnamoyl chloride according to the procedure described for the preparation of D37. MS: m/z ($MH^+$) 436/438.

**Example 163**

**(E)-3-(2-Chloro-phenyl)-1-[6-(2-piperidin-1-yl-ethoxy)-5-trifluoromethyl-2,3-dihydro-indol-1-yl]-propenone (E163)**

The title compound was prepared from 6-(2-piperidin-1-yl-ethoxy)-5-trifluoromethyl-2,3-dihydro-1H-indole (D64a) and 2-chlorocinnamoyl chloride according to the procedure described for the preparation of D37. MS: m/z ($MH^+$) 479/481

**Example 164**

**(E)-3-(2-Chloro-phenyl)-1-[6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E165)**

The title compound was prepared from 6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-1H-indole (D64b) and 2-chlorocinnamoyl chloride according to the procedure described for the preparation of D37. MS: m/z ($MH^+$) 411/413.

**Example 165**

**(*E*)-1-[5-Bromo-6-(2-piperidine-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2-chlorophenyl)propenone (E165)**

The title compound E165 was prepared from 2-chlorocinnamoyl chloride and 5-bromo-6-(2-piperidin-1-ylethoxy)-2,3-dihydro-1-indole (D55) according to the procedure described for the preparation of D37. Thus, 2-chlorocinnamoyl chloride (0.07 g, 1.1 eq.) was added over 10 minutes to a mixture of 5-bromo-6-(2-piperidin-1-ylethoxy)-2,3-dihydro-1-indole (D35) (0.10 g, 0.31 mmol) and pyridine (0.5 ml) in DCM (10 ml) at 0°C. The reaction mixture was stirred for a further 20 min. at 0°C then water (50 ml) was added and the mixture was extracted with DCM (3 x 75 ml). The organics were combined, dried ($MgSO_4$) and evaporated *in vacuo*. The solid residue was purified by column chromatography on silica gel (eluting with 5% methanol/DCM). Further purification was necessary to remove some de-brominated bi-product by preparative HPLC (Supelco Supersil ABZ+, using 0.01% TFA in a gradient of 10% - 90% $CH_3CN$ in $H_2O$) to yield the trifluoroacetate salt of the title compound (E37) as a yellow solid (0.03 g, 20%). $^1H$ (250MHz, $CD_3OD$) δ 8.18 (1H, d, *J* 15.5 Hz), 8.13 (1H, br. s), 7.95 (1H, m), 7.46 (4H, br. m), 7.13 (1H, d, *J* 15.5 Hz), 4.45 (4H, br. m), 3.80 (2H, br. D, *J* 11 Hz), 3.66 (2H, br. m), 3.28 (4H, br. m), 1.95 (4H, br. m), 1.55 (2H, br. m). MS: m/z ($MH^+$) 489/491.

**Example 166**

**(*E*)-1-[5-Bromo-6-(2-piperidine-1-ylethoxy)-2,3-dihydroindol-1-yl]-3-(2,3,5-trifluorophenyl)propenone (E166)**

The title compound (E166) was prepared according to the procedure described for D37 starting from 2,3,5-trifluorocinnamoyl chloride and 5-bromo-6-(2-piperidin-1-ylethoxy)-2,3-dihydro-1*H*-indole (D35). MS: m/z ($MH^+$) 509/511.

**Example 167**

**(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-piperazin-1-ylethoxy)-2,3-dihydroindol-1-yl]propenone (E167)**

4-(2-{1-[(*E*)-3-(2-Chlorophenyl)allanoyl]-5-methoxy-2,3-dihydro-1*H*-indol-6-yloxy}ethyl)piperazine-1-carboxylic acid *tert*-butyl ester (D52) (1.05 g) was dissolved in DCM (60 ml) and trifluoroacetic acid (30 ml) added. The reaction mixture was stirred at room temperature for 2 h then concentrated *in vacuo* and the residue partitioned between DCM (100 ml) and saturated sodium bicarbonate solution(175 ml). The aqueous layer was re-extracted with chloroform (50 ml x 2) and the combined organics concentrated *in vacuo* and azeotroped with methanol. The crude compound was purified by column chromatography on silica gel eluting with DCM to 10% methanol/DCM to 15% methanol in DCM containing 1.5% ammonia to give the title compound (E167) as a yellow foam (0.80 g, 93%). MS: m/z ($MH^+$) 442/444.

**Example 168**

**(*E*)-3-(2-Chlorophenyl)-1-(6-{2-[4-(3,3-dimethoxypropyl)-piperazin-1-yl]-ethoxy}-5-methoxy-2,3-dihydroindol-1-yl)propenone (E168)**

(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-piperazin-1-ylethoxy)-2,3-dihydro-indol-1-yl]propenone (E167) (0.150 g) was dissolved in N-methylpyrolidine (3.5 mL) and treated with diisopropylethylamine (0.07 mL) and 3-bromo-propionaldehyde dimethyl acetal (0.05 mL). The mixture was heated at 120°C for 15 hours, allowed to cool to room temperature and passed through a SCX column (Isolute R Flash SCX-2, 5 g/25 ml column reservoir, International Sorbant Technology) eluting with methanol followed by 10% ammonia/methanol. The ammonia/methanol fractions were combined and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with DCM to 3% methanol/DCM to give the title compound (E168) as a yellow oil (0.047 g, 25%).

$^1$H (400 MHz,$CDCl_3$) δ 1.80 (2H, br q), 2.41 (2H, t, J 7.6 Hz), 2.50 (4H, br s), 2.62 (4H, br s), 2.86 (2H, t, J 5.6 Hz), 3.19 (2H, t, J 8.0 Hz ), 3.32 (6H, s), 3.83 (3H, s), 4.20 (2H, t, J 5.6 Hz), 4.27 (2H, t, 8.4 Hz), 4.44 (1H, t J 5.6 Hz), 6.74 (1H, s), 6.84 (1H,d, J 15.2 Hz), 7.29 (2H, m), 7.42 (1H, m), 7.63 (1H, m), 8.15 (2H, m). MS: m/z ($MH^+$) 544/546.

**Example 169**

**(*E*)-1-[5-Bromo-6-(1-methylpiperidin-4-ylmethoxy)-2,3-dihydroindol-1-yl]-3-(2-chlorophenyl)propenone (E169)**

The title compound was prepared from 5-bromo-6-(1-methylpiperidin-4-ylmethoxy)indoline[1] and 2-chlorocinnamoyl chloride according to the procedure described for the preparation of D37. Thus, 2-Chlorocinnamoyl chloride (0.24 g, 1.1 mmol) in DCM (10 ml) was added dropwise over 10 min. to 5-bromo-6-(1-methylpiperidin-4-ylmethoxy)indoline[1] (0.35 g, 1.1 mmol) and pyridine (0.5 ml) dissolved in DCM (20 ml) at 0°C. The reaction mixture was warmed to room temperature over 20 minutes and then poured into water (100 ml). The mixture was then extracted with DCM (3 x 100 ml). The combined extracts were washed with water (150 ml) and dried ($MgSO_4$) and evaporated *in vacuo* to give the crude product as an orange oil. This was purified by column chromatography on silica gel eluting with 1% ammonia and 5% MeOH in DCM) to give the title compound (E48) as a gum. This was converted to the oxalate salt (0.39 g, 73%). $^1$H (250 MHz, MeOD) δ 8.07 (1H, s), 8.06 (2H, m), 7.98 (1H, d, J 15.2 Hz), 4.39 (2H, br t, J 8.4 Hz), 3.94 (2H, d, J 6.0 Hz), 3.39 (2H, br d, J 12.0 Hz), 3.14 (2H br t, J 8.4 Hz), 2.93 (2H, br m), 2.72 (3H, s), 2.01 (3H, br m), 1.62 (2H, br d, J 12.0 Hz). MS: m/z ($MH^+$) 489/491.

**Example 170**

**(E)-3-(2-Chloro-phenyl)-1-[6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-pyrrolo[3,2-c]pyridin-1-yl]-propenone (E170)**

The title compound was prepared from 6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine (D67) and 2-chlorocinnamoyl chloride according to the procedure described for the preparation of D37. MS: m/z ($MH^+$) 412/414.

**Example 171**

**(E)-3-(2-Chloro-phenyl)-1-[5-fluoro-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-indol-1-yl]-propenone (E171)**

The title compound was prepared from 5-fluoro-6-(2-piperidin-1-yl-ethoxy)-2,3-dihydro-1H-indole (D73) and 2-chlorocinnamoyl chloride according to the procedure described for the preparation of D37. MS: m/z ($MH^+$) 429/431.

1. Gaster *et al.*, WO-98/50346.

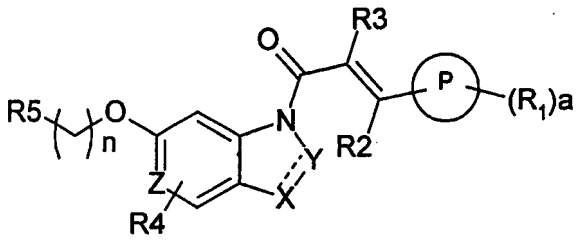
**Pharmacological data**

**[$^3$H]-mesulergine binding to rat or human 5-$HT_{2C}$ clones expressed in HEK 293 cells in vitro**

Compounds can be tested following the procedure outlined in WO 94/04533. The compounds of the Examples had pKi values in the range 7.5 - 9.8 in human cells.

Claims:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:




(I)

in which:

P is phenyl or naphthyl;

$R^1$ is halogen, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, $C_{1-6}$alkylthio, hydroxy, amino, mono- or di-$C_{1-6}$alkylamino, nitro, CN, $CF_3$, $OCF_3$, aryl, aryl$C_{1-6}$alkyl, aryl$C_{1-6}$alkyloxy or aryl$C_{1-6}$alkylthio;

a is 0, 1, 2, 3, 4 or 5;

$R^2$ and $R^3$ are independently hydrogen or $C_{1-6}$alkyl;

$R^4$ is hydrogen, halogen, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, aryl, cyano, halo$C_{1-6}$alkyl or halo$C_{1-6}$alkoxy;

Z is carbon or nitrogen;

$R^5$ is either:

(i) a group $NR^6R^7$ where $R^6$ and $R^7$ are independently hydrogen, optionally substituted $C_{1-6}$alkyl or aryl$C_{1-6}$alkyl; or

(ii) an optionally substituted N-linked heterocycle; or

(iii) an optionally substituted C-linked heterocycle;

n is 0, 1, 2 or 3 subject to the proviso that n is not 0 when $R^5$ is a group (i) or (ii);

------ represents a single or double bond;

X and Y are independently $CR^8R^9$ (when ------ represents a single bond) or X and Y are independently $CR^{10}$ (when ------ represents a double bond) wherein $R^8$, $R^9$ and $R^{10}$ are indepedently hydrogen or $C_{1-6}$alkyl.

2. A compound according to claim 1 in which P is phenyl.

3. A compound according to claim 1 or claim 2 in which $R^5$ is a group (ii) in which the N-linked heterocycle is an unsubstituted piperidine ring or an unsubstituted morpholine ring.

4. A compound according to any of the preceding claims wherein when a is not 0, $R^1$ is fluoro, chloro, bromo, methyl, methoxy or $OCF_3$.

5. A compound according to any of the preceding claims wherein a is 0, 1, 2, or 3.

6. A compound according to any of the preceding claims wherein $R^2$ and $R^3$ are both hydrogen.

7. A compound according to any of the preceding claims wherein Z is carbon.

8. A compound according to any of the preceding claims wherein $R^4$ is hydrogen, chloro, bromo, methoxy or methyl.

9. A compound according to claim 7 or claim 8, in which Z is carbon and $R^4$ is a methoxy group at the 5 position of the indoline or indole ring.

10. A compound according to any of the preceding claims wherein when $R^5$ is a group of formula (i) or (ii), n is 2 or 3.

11. A compound according to any of the preceding claims wherein ------ represents a single bond.

12. A compound according to any of the preceding claims wherein both X and Y are $CH_2$.

13. A compound according to claim 1 which is:

(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-piperidin-1-ylethoxy)-2,3-dihydroindol-1-yl]propenone hydrochloride;
(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-morpholin-4-ylethoxy)-2,3-dihydro-indol-1-yl]propenone;

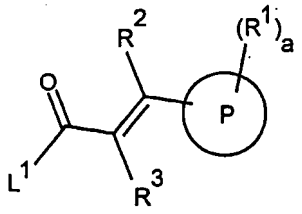
(*E*)-3-(2-Chlorophenyl)-1-[5-methoxy-6-(2-pyrrolidin-1-ylethoxy)-2,3-dihydroindol-1-yl]propenone;
(E)-3-(2-Chloro-phenyl)-1-{5-methoxy-6-[2-(2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl)-ethoxy]-2,3-dihydro-indol-1-yl}-propenone;
(E)-1-{6-[2-(tert-Butyl-methyl-amino)-ethoxy]-5-methoxy-2,3-dihydro-indol-1-yl}-3-(2-chloro-phenyl)-propenone;
(E)-3-(2-Chloro-phenyl)-1-[6-(2-diethylamino-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-propenone;
(E)-3-(2-Chloro-phenyl)-1-[6-(2-dimethylamino-ethoxy)-5-methoxy-2,3-dihydro-indol-1-yl]-propenone;

or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 1 which is a compound shown in Table 1, Table 2, Table 3 or Table 4 or a pharmaceutically acceptable salt thereof.

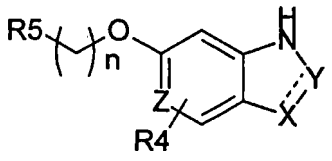
15. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises either:

(a) the coupling of a compound of formula (II):



(II)

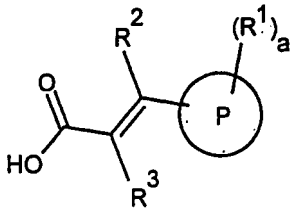
in which $R^1$, $R^2$, $R^3$, P and a are as defined in formula (I) and $L^1$ is a leaving atom with a compound of formula (III):



(III)

in which X, Y, ------, $R^4$, $R^5$, Z and n are as defined in formula (I); or

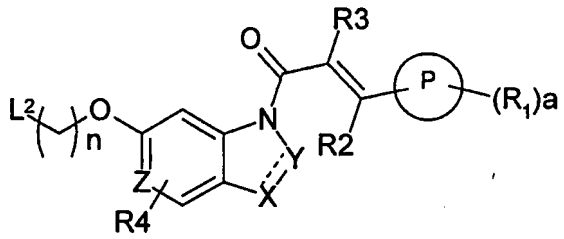
(b) the coupling of a compound of formula (IV)



(IV)

in which $R^1$, $R^2$, $R^3$, P and a are as defined in formula (I) with a compound of formula (III) as defined in process (a) in the presence of suitable amide coupling reagent; or

(c) when $R^5$ is a group (i) or (ii), the coupling of a compound of formula (V)



(V)

in which X, Y, ------, $R^1$, $R^2$, $R^3$, $R^4$, Z, P, a and n are as defined in formula (I) and $L^2$ is a leaving group, with a compound of formula (VI)

H - $NR^6R^7$ or H - (N-linked heterocycle)

(VI)

in which N-linked heterocycle, $R^6$ and $R^7$ are as defined in formula (I);
and optionally thereafter for either process (a),(b) or (c)

- removing any protecting groups; and/or
- converting a compound of formula (I) into another compound of formula (I); and/or

- forming a pharmaceutically acceptable salt.

16. A process as claimed in claim 15, wherein $L^1$ is chloro.

17. A process as claimed in claim 15 or claim 16, wherein the reaction of a compounds of formulae (II) and (III) is carried out in an inert solvent such as dichloromethane optionally in the presence of a base such as triethylamine or pyridine.

18. A process as claimed in claim 15, wherein $L^2$ is a halogen, mesylate or tosylate.

19. A process as claimed in claim 15 or 18, wherein the reaction of a compound of formulae (V) and (VI) is carried out in an inert solvent such as dimethylformamide, optionally in the presence of sodium iodide and a base such as potassium carbonate.

20. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 14 and a pharmaceutically acceptable carrier or excipient.

21. A process for preparing a pharmaceutical composition according to claim 20, the process comprising mixing a compound according to any one of claims 1 to 14 and a pharmaceutically acceptable carrier or excipient.

22. A compound according to any one of claims 1 to 14 or a composition according to claim 20 for use in therapy.

23. A compound according to any one of claims 1 to 14 or a composition according to claim 20 for use in treatment or prophylaxis of CNS and other disorders.

24. A compound according to any one of claims 1 to 14 or a composition according to claim 20 for use in treatment or prophylaxis of anxiety and/or depression.

25. The use of a compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, or a composition according to claim 20, in

the manufacture of a medicament for the treatment or prophylaxis of CNS and other disorders.

26. The use as claimed in claim25, wherein the medicament is for the treatment or prophylaxis of anxiety and/or depression.

27. A method of treatment or prophylaxis of CNS and other disorders, in mammals including humans, which comprises administering to a patient in need thereof a safe and therapeutically effective amount of a compound according to any of claims 1 to 14, or a composition according to claim 20.

28. A method according to claim 27, wherein the disorder is anxiety and/or depression.

# INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/08 C07D401/12 C07D403/12 C07D403/14 C07D413/12
C07D417/12 C07D493/10 A61K31/4453 A61K31/496 A61K31/5377
//(C07D493/10,317:00,221:00),(C07D493/10,319:00,221:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data, PAJ

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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| 18 December 2001 | 27/12/2001 |

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